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PART I: REACTIONS OF NUCLEOPHILES WITH PYRIDINIUM IONS CYANIDE ION REACTIONS WITH SOME PYRIDINIUM IONS PART II: SODIUM BOROHYDRIDE REDUCTION OF THE METHYL IODIDE SALTS OF FORMYL AND BENZOYLPYRIDINE OXIMESAND OXIME, METHYL ETHERS

GEORGE JAMES GAUTHIER

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SODIUM BOROHYDRIDE REDUCTION OF THE METHYL IODIDE SALTS OF FORMYL- AND BENZOYLPYRIDINE OXIMES AND OXIME, METHYL ETHERS.

BY

GEORGE JAMES GAUTHIER

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Paul R. Jones

F. L. Pilar

James D. Morrison

A. E. Taeri

Kenneth K. Andersen

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Date

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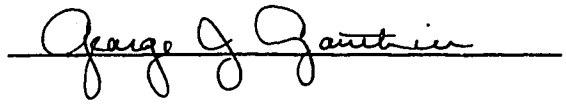

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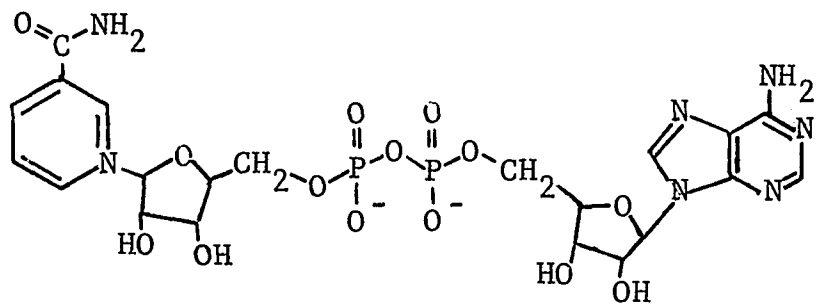
PART I

REACTIONS OF NUCLEOPHILES WITH PYRIDINIUM IONS. CYANIDE ION REACTIONS WITH SOME PYRIDINIUM IONS.

INTRODUCTION

The increasing interest in the nature and reactivity of dihydropyridines during recent years has been a direct result of two major occurrences. The first was the discovery that the important coenzyme nicotinamide adenine dinucleotide (1)(NAD) was physiologically active by its reduction to a 1, 4-dihydropyridine. The structure of the reduced nicotinamide moiety of NADH (1a) was determined, only after considerable controversy[24-28], by the use of deuterium labelling experiments[27,29] and by a comparison of the ultraviolet absorption spectrum of NADH with that of the model compound 1-methyl-3-carbamoyl-1,4-dihydropyridine derived from the sodium dithionite reduction of 1-methyl-3-carbamoylpyridinium halide (15).[27,29]



Nicotinamide Adenine Dinucleotide (NAD)

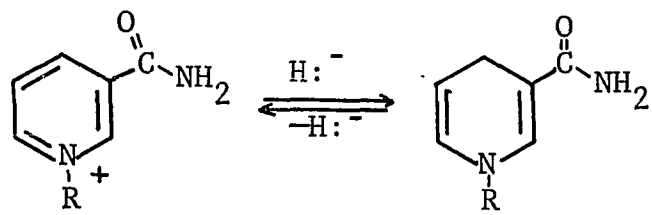
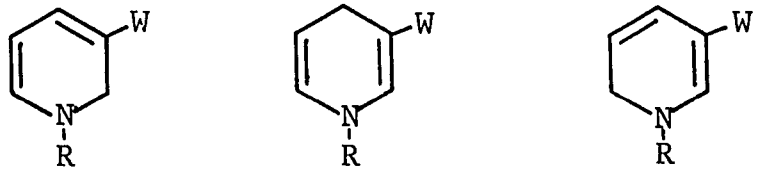


Figure 1: Oxidized (1) and Reduced (1a) Forms of the Pyridinium Ring of NAD

Typical of the enzymatic conversions in which NAD participates are the in vivo and in vitro oxidations of alcohols to aldehydes or ketones.[1] The reduced form (NADH) participates in the reduction of aldehydes or ketones to alcohols.[1,27] These important reactions alone provide sufficient reason for reexamining the original questions raised about pyridinium ion chemistry, i.e., are the factors which lead to the preferential formation of the 1,4-dihydropyridine isomer primarily steric, electronic, thermodynamic, or some combination of these.[13] These questions, and their solution, acquire special significance when one considers the possibility that activity differences between NAD (NADH) and its analogs may provide a method for changing and establishing evolutionary patterns on a molecular level.[1]

The second important occurrence was the successful and general application of modern instrumental methods of analysis to the structure determination of dihydropyridines. As recently as 1957, the determination of the structure of dihydropyridines could be done only by the use of tedious methods. Ultraviolet spectroscopy provided the most convenient method for differentiating between the possible stable 3-substituted dihydropyridines, i.e., the 1,2-dihydro-, 1,-4-dihydro-, and 1,6-dihydropyridines. The structures of the dihydropyridines from sodium borohydride reductions [1,14,16,19,33-35], sodium dithionite reductions[1,14-16,19,26,29-33], reactions with cyanide ion[1,16,19,20,22,24,30,31] Grignard reactions[62], and reaction with hydroxide ion[31] have been successfully elucidated using ultraviolet absorption spectroscopy.



1,2-dihydro	1,4-dihydro	1,6-dihydro
380-420 mμ	320-360 mμ	240-280 mμ 320-360 mμ

Figure 2

Ultraviolet Absorption Spectra of
3-Substituted Dihydropyridines

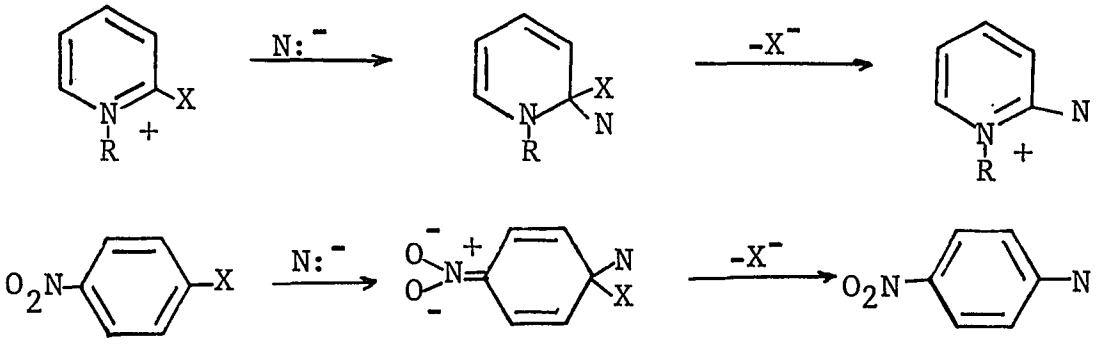
In general[2,19], a 1,4-dihydropyridine with an electron-withdrawing substituent on the 3-position exhibits a single absorption maximum in the range 320-360 mμ. The corresponding 1,6-dihydropyridine exhibits a maximum in the same range as the 1,4-dihydropyridine but is differentiated from the 1,4-dihydropyridine isomer by having an additional maximum in the range 240-280 mμ. The 1,2-dihydropyridine exhibits a single maximum at longer wavelength than the corresponding 1,4- or 1,6-dihydropyridine, usually in the range 380-420 mμ.

A few applications of nuclear magnetic resonance spectroscopy to the determination of structure of dihydropyridines have been reported[14,21,29], although the number of such examples is small. Used together, ultraviolet and nuclear magnetic resonance spectroscopy provide a technique for the rapid determination of structure of most dihydropyri-

dines and an important aspect of this thesis is a demonstration of the ease with which many reactions of pyridinium ions and dihydropyridines can be followed using ultraviolet and nuclear magnetic resonance spectroscopy as complimentary techniques.

The preparation and reactions of pyridinium salts are the subjects of reviews by Lyle[13], Shaw[2], Duffin[5], Kosower[1], and Evans.[73] Pyridinium salts exhibit almost no tendency towards reaction with electrophiles but undergo reaction readily with numerous nucleophiles including acetylide ions[61], stabilized carbanions[60], amines[1], ions such as hydroxide, cyanide, borohydride and dithionite, and the Grignard reagents previously mentioned.

The reactions of nucleophiles with pyridinium ions also provide suitable models for studying the steric, electronic, and other factors involved in the bimolecular nucleophilic substitution reactions (S_NAr_2) of nitrobenzenes[6] and some heteroaromatic systems.[13,45] Studies of the S_NAr_2 reactions of these compounds indicate that they proceed through a transition state or intermediate sigma complex of the type illustrated below. Usually, the intermediate species are relatively short lived and it is difficult to study their properties. The addition of a nucleophile to a pyridinium ion, however, provides a stable dihydropyridine under certain conditions and consequently, studies of nucleophilic attack on aromatic ststems can be studied in a stepwise fashion.[12,13]



It was obvious very early in this work that although a wide variety of suitable pyridinium salts could be obtained readily, the choice of the nucleophile to be used would greatly determine the variety and type of reactions which could be studied. Some nucleophiles were difficult to handle quantitatively on a routine basis (Grignard reagents), others produced dihydropyridines which could not be readily characterized (hydroxide), and others were reactive with the electron-withdrawing substituents attached to the pyridinium ring (ethoxide, borohydride).

The study of the reactions of cyanide ion with pyridinium ions, however, appeared particularly attractive for several reasons. Cyanide ion is an excellent nucleophile[63] and is easily handled as its sodium or potassium salt in a variety of solvents. The cyanide addition compounds of NAD and a large number of pyridinium salts had been reported and characterized[1,16,19,20,22,24,30,31], and these derivatives were ordinarily stable, crystalline compounds. Furthermore, the 4-cyano-1,4-dihydropyridines were known to undergo a reversible reaction under certain conditions to regenerate cyanide and pyridinium ions.[19,20] The 4-cyano-1,4-dihydropyridines had also been used as models for a comparison of spectroscopic properties[19,28,30] with the cyanide adduct of NAD. For these reasons, conclusions concerning the mechanism of formation, properties, and reactivity of cyanide adducts of ordinary pyridinium salts acquired very special importance.

Prior to 1957, numerous examples of nucleophilic addition to pyridinium salts had been reported but little or no attempt had been made to correlate the mass of data then available. Kosower[39] provided a seemingly attractive means for rationalizing that data. A review of the important aspects

of Kosower's work is needed for this discussion though the reader is referred to his paper[39] and recent book[1] for a more thorough treatment. It had been observed that the site of attack of many nucleophiles upon pyridinium ions appeared to be primarily dependent on the nature of the nucleophile and not upon the nature of the pyridinium substrate or steric effects. The hydride from borohydride ion, the carbanion from Grignard reagents, and the hydroxyl ion were known to add to a position adjacent to the positive nitrogen while cyanide ion, carbanions, and the hydride via dithionite reduction were known to add to the 4-position of the pyridinium ion. Kosower's basic proposal that "nucleophiles which form charge-transfer complexes easily, or which might be expected to do so, add at the 4-position, while those nucleophiles which probably do not form complexes, or do so only to a very limited extent, add at the 2-position"[1], was based on these generalizations. His estimate of the ability of a nucleophile to form a charge-transfer complex was based, in part, on the electrode potential (E°) of the electron donor in the reaction

$$2X:^- \rightleftharpoons X_2 + 2e^-$$

The E° value for cyanide was estimated from the data of Hawthorne[63] who had considered the linear relationship of the oxidation potential of the nucleophiles and their nucleophilic constants $\underline{n}$ in the Swain-Scott equation. This linear relationship was first studied by Edwards.[64]

Kosower's thesis was criticized[61] on the grounds that acetylide ions added to the 2-position of N-acylpyridinium ions though they would be expected to complex with the pyridinium ring and attack the 4-position. He answered that this was not a serious criticism since "Implicit in the notion[39]

was the requirement of ambident nature of the ion (or molecule) acting as addend, so that electrostatic attraction of the positive charge in the pyridinium ring and the negative charge in the addend could provide the means for association, while juxtaposition of a nucleophilic center in the addend with the 4-position of the ring would lead to addition at the 4-position. In all cases where ambidental combination of negative charge and nucleophilicity is present (e.g. enolate ions, sulfoxylate, sulfite), 4-addition appears to be preferred."[1] Thus Kosower, by proposing a duality of mechanism, could rationalize a few of the unusual nucleophilic additions to pyridinium ions to give 1,4-dihydropyridines, but his proposal did not provide a rationale for many other peculiar nucleophilic additions of other types of pyridinium salts.

The nucleophilic addition of cyanide ion to pyridinium ions might be expected to lead exclusively to 1,4-dihydro-pyridines[39], however, the reaction of cyanide with 1-alkoxypyridinium salts appeared to be influenced by the same factors involved in the sodium borohydride reduction of pyridinium salts.[13] Sodium borohydride has been shown to undergo reaction at the 2- and 6-positions of the pyridinium ring primarily with some addition at the 4-position of the pyridinium ring depending on the size of the N-substituent[11] (Figure 3). An increase in the size of the N-substituent was shown to result in larger 1,4-/1,2-dihydropyridine ratios.[11]

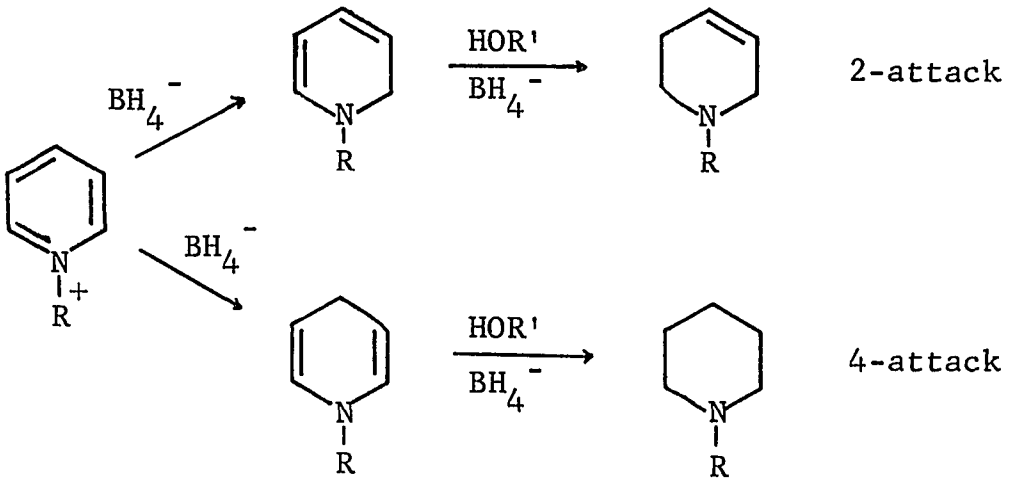
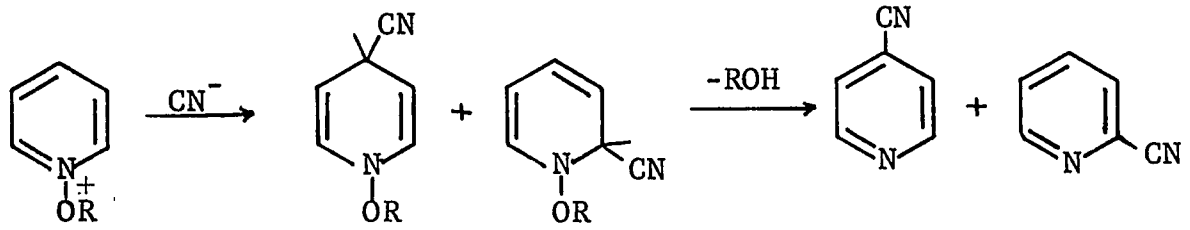
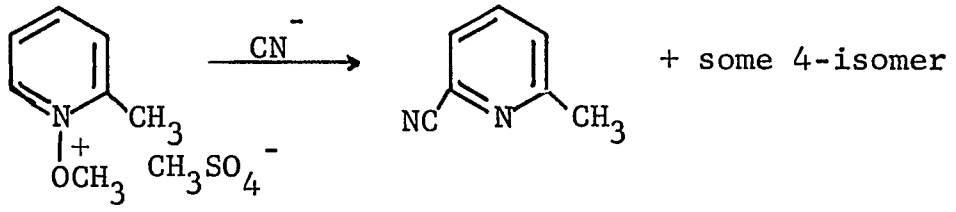


Figure 3. Effect of Size of N-Substituent on the Site of Attack of Borohydride on Pyridinium Ions.

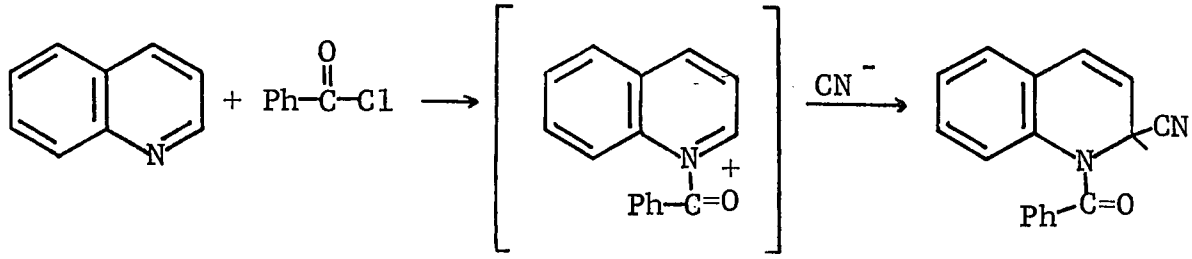
R	% 4-attack	% 2-attack
CH_3	0	100
$CH_2CH_2CH_2CH_3$	5	95
CH_2Ph	12	88
$CH(CH_3)_2$	28	72

Similarly, the reaction of 1-alkoxypyridinium ions[41-42] with cyanide ion gave 2- and/or 4-cyanopyridine depending upon the steric crowding about the nitrogen. The study of this reaction was facilitated by the irreversible nature of the reaction due to the loss of the elements of alcohol from the addition product.[13] The structure of the products could be determined by a comparison with authentic samples of 2- and 4-cyanopyridine.





The reaction of cyanide ion in the formation of Reissert compounds (N-acyldihydroquinaldonitriles) with quinoline also seems to be contrary to predictions based on the "charge-transfer" orientation hypothesis. As indicated in the review by McEwen[46], the reaction of benzoyl chloride, quinoline (86), and potassium cyanide leads to a stable 2-cyano-1,2-dihydroquinoline (87).[46] Similarly, quinoline-1-oxide (88) reacts with benzoyl chloride and cyanide ion to form 2-cyanoquinoline (89). A 1,2-dihydroquinoline is the presumed intermediate and the reaction is nearly quantitative.[46]



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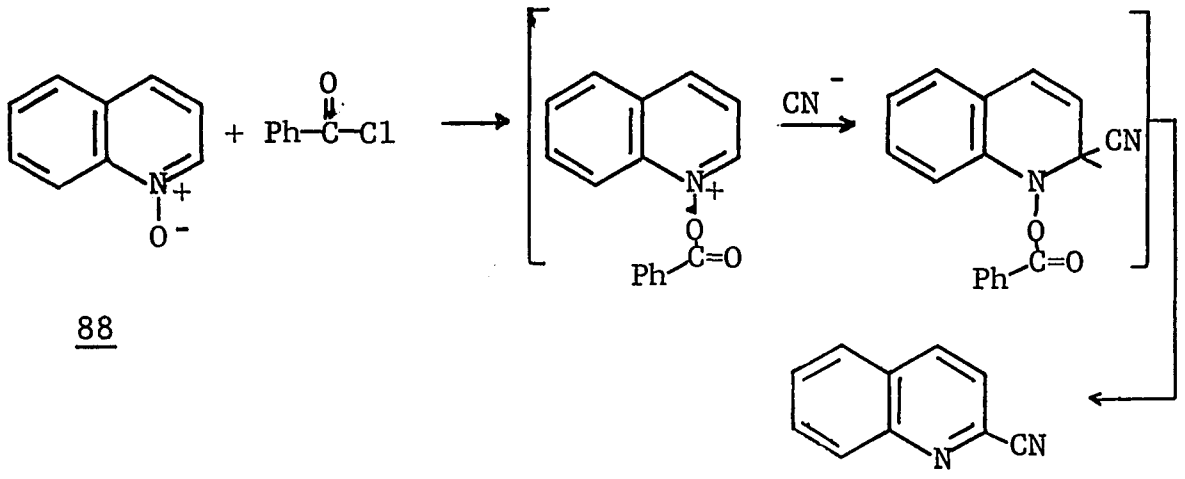

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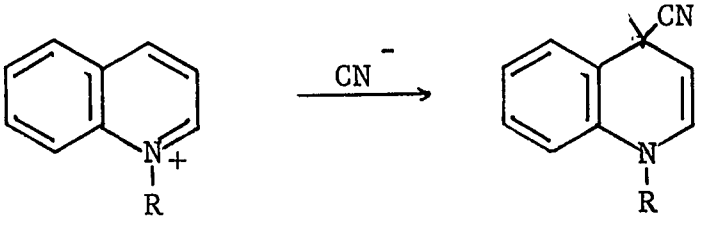
In contrast to these results, N-alkylquinolinium salts undergo reaction with cyanide ion giving only 1,4-dihydroquinolines.[47] No explanation for the differences in the sites of addition between N-acyl- and N-alkylquinolinium compounds has been reported.



Clearly, the site of reaction of nucleophiles with pyridinium ions and quinolinium ions cannot be predicted on the basis of the formation or lack of formation of a "charge-transfer" complex. The first part of this thesis describes some investigations of the reactions of cyanide ion with a number of pyridinium ions and the logical correlation of the nature of the products formed with the reaction conditions and structure of the reactants.

DISCUSSION AND RESULTS

The addition of cyanide ion to a pyridinium ion generally occurs only if the pyridinium ion is made very electrophilic by an electron-withdrawing group on the 3-position.[20,28] For this reason, a series of pyridinium salts with substituents of different electron-withdrawing strength on the 3-position were prepared for reaction with cyanide ion.

Preparation of Pyridines and Pyridinium Salts

Many of the pyridines and pyridinium salts required for this investigation had been reported in the literature and some of the pyridines were available from commercial sources. The sources of these starting materials are summarized in Table I. The formation of pyridinium ions by alkylation of the pyridine with methyl iodide and benzyl halide proceeded well; however, the reaction with 2,6-dichlorobenzyl chloride required more care because the presence of unreacted halide caused the products to be highly hygroscopic. Although many of the 2,6-dichlorobenzyl bromides were known[19-21,60], the chloride analogs were unknown.

Wallenfels' early studies[19,20] led to the prediction that pyridinium ions with 3- and 5-electron-withdrawing substituents should cause the initial reaction with cyanide ion to be irreversible at room temperature due to the high electrophilicity of the pyridinium ion. Improved syntheses of several 3,5-symmetrically disubstituted pyridines were developed and these compounds were quaternized using the methods described in the Experimental.

The synthesis of 3,5-dicarboxypyridine (51) from 3,5-

dimethylpyridine was accomplished in 39% yield by a simple oxidation reaction using potassium permanganate. Preparation of the acid chloride hydrochloride of 51 was accomplished by heating 51 and thionyl chloride. Treatment of the solid acid chloride hydrochloride with anhydrous methanol gave a 68% yield of 3,5-dimethoxycarbonylpyridine (52). The reaction of 52 and methyl iodide in acetone gave a 96% yield of 1-methyl-3,5-dimethoxycarbonylpyridinium iodide (53).

The reaction of the acid chloride hydrochloride of 51 with liquid ammonia gave a 92% yield of 3,5-dicarbamoylpyridine (54). The benzyl bromide salt (55) of 54 was prepared in 92% yield.

The methyl iodide salt (56) of commercially obtained 3,5-dicyanopyridine was prepared in 76% yield by allowing a solution of 3,5-dicyanopyridine and methyl iodide in acetone to stand at room temperature. These reactions are illustrated below.

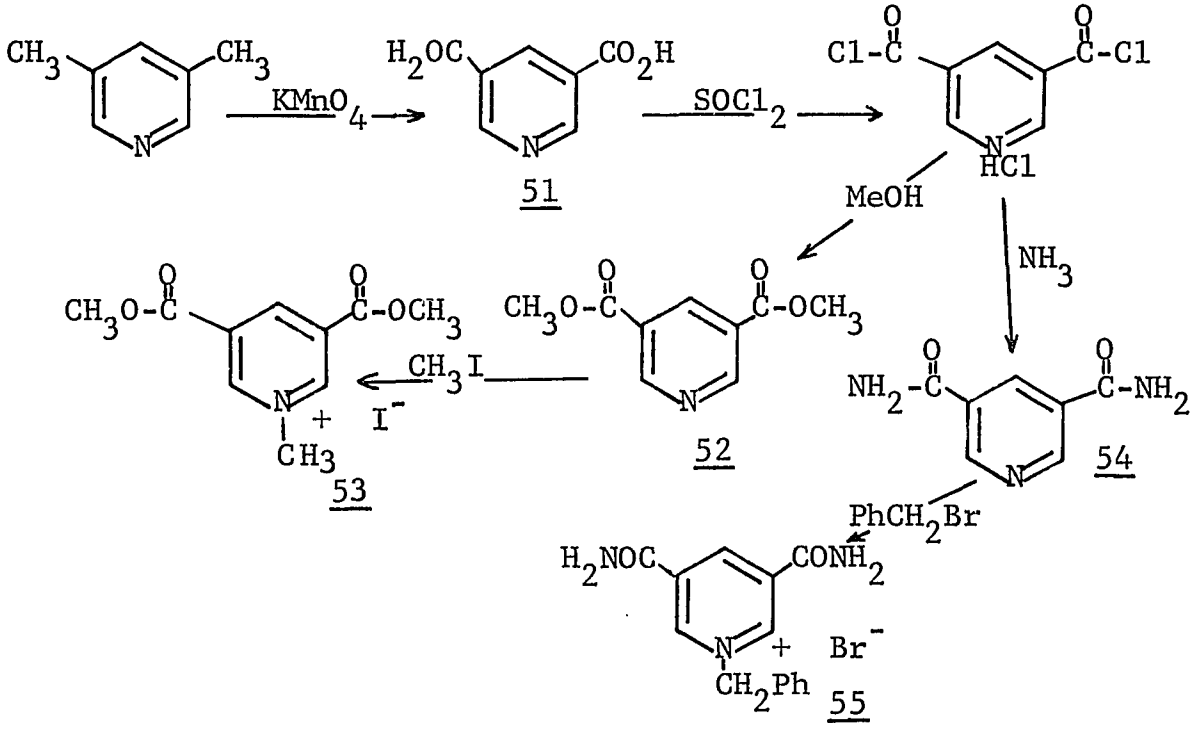
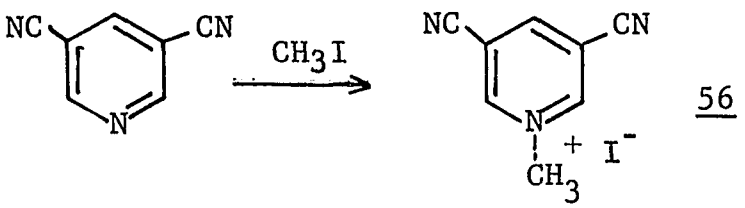


Figure 7. Synthesis of 3,5-Symmetrically Disubstituted Pyridines and Pyridinium Salts.



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Spectroscopic Properties of Pyridinium Salts

The infrared, ultraviolet, and nuclear magnetic resonance spectra of the pyridinium salts were determined for use in characterizing the pyridinium salts.

The pyridinium salts each exhibited a single maximum in the ultraviolet absorption spectrum in methanol at 262-287 mμ (Table III). Since only small differences are evident in the ultraviolet absorption spectra of a pyridine and that of the corresponding pyridinium ion, it can be concluded that the $\pi - \pi^*$ transitions are little affected by the quarternary salt formation. It was further evident that the nature of the 3-substituent had little effect on this electronic transition.[13] The ultraviolet absorption maxima of pyridinium salts were consistent, in all cases, with those values available from the literature.

The ultraviolet absorption spectrum of 1-methyl-3,5-dimethoxycarbonylpyridinium iodide (53) in methanol showed absorption maxima at 270 mμ (3.57), 277 mμ (3.65), and 350 mμ (2.46). The spectrum of 1-benzyl-3,5-dicarbamoylpyridinium bromide (55) in methanol showed a maximum at 268 mμ (3.66). The spectrum of 1-methyl-3,5-dicyanopyridinium iodide (56) in methanol showed maxima at 280 mμ (2.84), 288 mμ (2.91), and 348 mμ (3.66).

The nuclear magnetic resonance spectra of compounds 2-18 were determined in deuterium oxide and the δ-values and coupling constants (c.p.s.) are listed in Table IV.

Chemical shifts were determined relative to the sharp singlet assigned a δ -value of 4.75 p.p.m. (relative to tetramethylsilane) which appeared upon addition of a drop of H_2O to the deuterium oxide solution. Thus the values for chemical shifts are only approximate. The peak at 4.75 p.p.m. is attributed to absorption by the proton of DOH. Coupling constants (J) are in c.p.s. An examination of the spectra of seventeen pyridinium salts revealed the following general characteristics:

a) The resonance band of the protons of N-methyl groups of the methyl iodide salts was found as a sharp singlet at 4.59-4.80 p.p.m. The resonance band of the protons of the methylene group of the N-benzyl groups of the benzyl halide salts was found as a sharp singlet at 5.94-6.07 p.p.m. The resonance band of the protons of the methylene group of the N-(2,6-dichlorobenzyl) group was found as a sharp singlet at 6.28-6.38 p.p.m.

b) The proton on the 2-position of the pyridinium ring was influenced by its proximity to both the deshielding electron-withdrawing substituent on the 3-position and to the positively charged nitrogen and consequently exhibited the strongest downfield shift (to higher δ -values) of all the ring protons. The resonance band of the 2-proton of pyridinium salts in which the 3-substituent was methoxycarbonyl, ethoxycarbonyl, acetyl, carbamoyl, and cyano was at 9.39-9.69 p.p.m. and gave a singlet, the band width of which suggested unresolved splitting by some other ring proton(s). Attempts to resolve this splitting were unsuccessful. The signal at 9.09-9.20 p.p.m. in the spectra of 3-benzoylpyridinium salts was found as a singlet or doublet and was assigned to the 2-proton.[21]

The upfield shift of the 2-proton of the 3-benzoylpyridinium salts relative to that of other 3-carbonylpyridinium salts can be rationalized if one considers that the carbonyl group and pyridinium ring are both electron attracting. The plane of the 3-benzoyl group could be approximately perpendicular to that of the pyridinium ring reducing the competitive interaction of the two electron-withdrawing systems. This conformation would place the 2- and 4-protons of the pyridinium ring in the shielding cone of the benzoyl phenyl group causing the upfield shift.[8]

c) The resonance band of the proton on the 4-position was found at 8.80-9.25 p.p.m. as a doublet with additional unresolved splitting or as a resolved sextet. The doublet resulted from coupling of the 4-proton with the adjacent 5-proton, J_{45} = 7.8-8.8 c.p.s. The sextet of the 4-proton presumably resulted from the additional small coupling of the 4-proton with the 2- and 6-protons, J_{24} and J_{46} = 1.6-1.8 c.p.s. The protons on the 4-position of the 3-benzoylpyridinium salts were shifted slightly upfield relative to the 4-proton of other 3-carbonylpyridinium salts for the previously described reasons.

d) Due to the proximity of the positively charged ring nitrogen, the resonance of the proton on the 6-position appeared slightly downfield from that of the 4-proton. The band for the 6-proton appeared as a doublet with further unresolved splitting or as a sextet at about 9.13-9.37 p.p.m. The doublet resulted from coupling of the 6-proton with the adjacent 5-proton, J_{56} = 5.5-6.8 c.p.s. Sextets presumably resulted from an additional small coupling of the 4-proton with the 2- and 4-protons, J_{26} and J_{46} = 1.6 c.p.s. The observation that J_{45} was larger than J_{56} in all cases appears to be of general utility in the assignment of the 4- and 6-

protons of pyridinium salts. Similar observations have been made for isolated examples of 3-substituted pyridinium ions.[21,67]

e) The resonance band of the proton on the 5-position was the furthest upfield of the aromatic hydrogens. The resonance band was found at 8.24-8.53 p.p.m. as a well defined quartet due to the coupling of the 5-proton with the adjacent 4- and 6-protons previously described.

f) The ring protons of the 3,5-disubstituted pyridinium salts exhibited relatively simple spectra compared to the 3-substituted pyridinium salts. The δ-values and coupling constants for these protons can be found in Table IV.

The Reaction of Cyanide Ion with Pyridinium Ions. Preparation and Properties of 4-Cyano-1, 4-dihydropyridines (28-44).

The reaction of cyanide ion with pyridinium ions has been reported to lead, in all cases, to 4-cyano-1,4-dihydropyridines.[1,16,19,20,22,24,30,31] These products were characterized primarily by their ultraviolet absorption spectra which consisted of a single maximum at 320-360 mμ. Such an ultraviolet absorption spectrum has been shown to be characteristic of a 1,4-dihydropyridine.[2,19] In a few cases, the structural assignments were made using nuclear magnetic resonance spectroscopy.[21] An excellent review of these reactions has been published by Wallenfels.[19,20] Interestingly, the reaction of cyanide ion with 3-substituted pyridinium ions is reversible.[20] The degree of dissociation of the 3-substituted 4-cyano-1,4-dihydropyridine was found to be in the order $-CO_2H > -CO_2R > -CONH_2 > -COCH_3$.[20]

There are no reported examples of the successful reaction of cyanide ion with simple unsubstituted pyridinium ions, with alkyl-substituted pyridinium ions, or with pyridinium ions substituted with electron-withdrawing groups on the 2- and/or 4-positions. These facts seem to imply two prerequi-

sites for the successful addition of cyanide ion to pyridinium ions.

First, the pyridinium ion must be made strongly electrophilic by a substituent capable of electron-withdrawal. Second, electron-withdrawing substituent must be located on the pyridinium ion in a position such that the dihydropyridine, once formed, will be stabilized by the substituent. For maximum stabilization, the ring substituent apparently must be located at the 3- or 5-position.

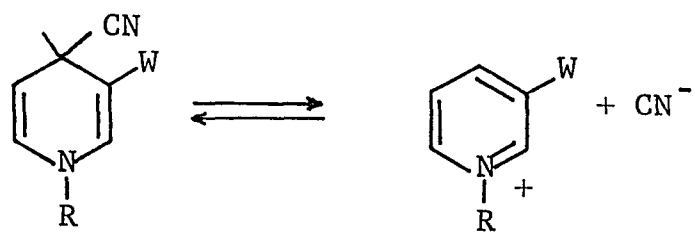
Prior to the investigation of the nature of the intermediates formed in the reactions of cyanide ion with pyridinium ions, a study of the properties of the products of the reactions was undertaken. It was hoped that an intimate knowledge of the infrared, ultraviolet, and nuclear magnetic resonance spectra of the 4-cyano-1,4-dihydropyridines would provide a basis for the structure determination of the previously unknown intermediates formed in the reaction.

A number of 4-cyano-1,4-dihydropyridines were prepared and characterized during these studies. Their physical properties are described in Table V.

The infrared spectra of seventeen 4-cyano-1,4-dihydropyridines have been correlated in Table VIII in order to emphasize absorption bands characteristic of each member of the series of 4-cyano-1,4-dihydropyridines. The 4-cyano group was characterized by a weak to medium intensity absorption band at 2220-2230 $cm.^{-1}$. This band is at slightly lower frequency ($cm.^{-1}$) than the band for most simple unconjugated nitriles which absorb in the range 2240-2260 $cm.^{-1}$.[7] The conjugated nitrile at the 3-position of 3,4-dicyano-1,4-dihydropyridines (35-37) exhibits strong absorption at 2200-2205 $cm.^{-1}$ due to being attached to an enamine system. The only other important absorptions to be considered in this discussion

are the strong to very strong absorptions at 1680-1695 cm.$^{-1}$, and 1600-1630 cm.$^{-1}$. The former absorption is apparently a result of the 5,6-double bond enamine system[15] and the latter results from the 2,3-double bond in conjugation with both the electron-withdrawing 3-substituent and the other enamine system. For example, the model compound 1-benzyl-3-cyano-1,4-dihydropyridine (45)[15] absorbs at 1680 and 1605 cm.$^{-1}$. Hydrogenation of the 5,6-double bond was accompanied by loss of the former absorption and a shift of the latter absorption to 1630 cm.$^{-1}$.[15]

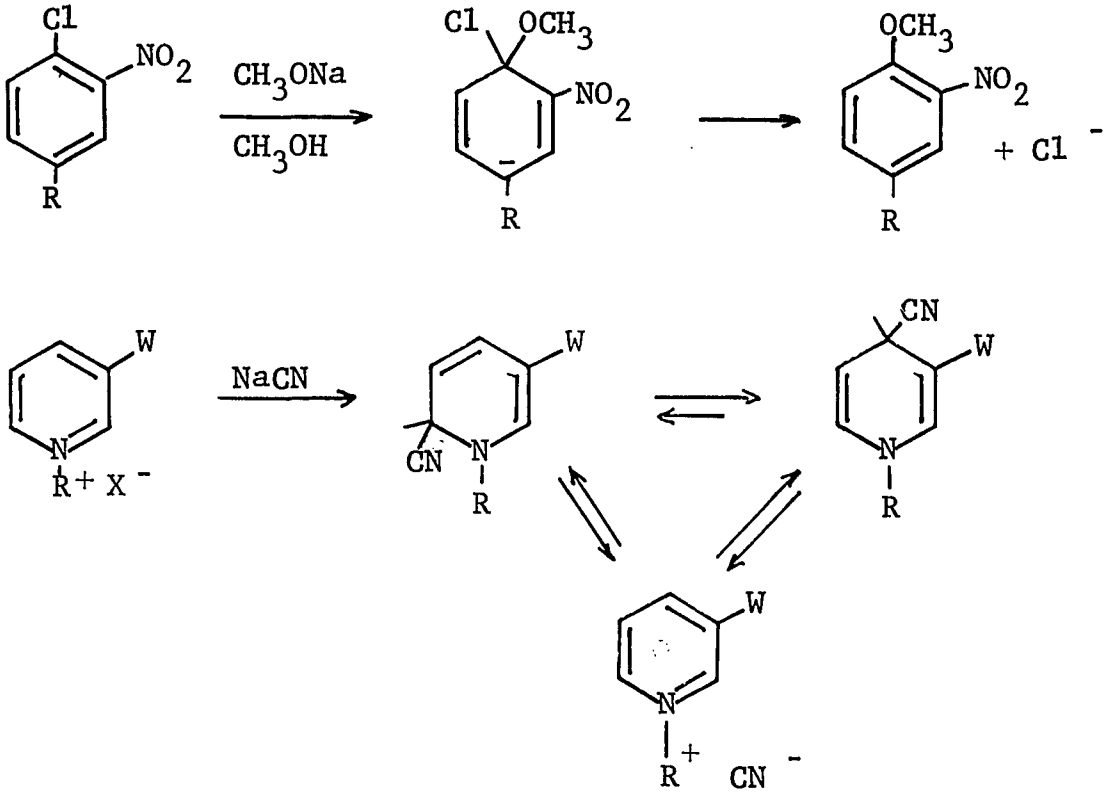
The intensity of the absorption band of the 4-cyano-1,4-dihydropyridine decreased as the polarity and hydrogen bonding power of the solvent increased. The decrease in intensity was accompanied by the appearance of a new absorption band at about 270 mμ. These changes are in agreement with the findings of Wallenfels[19,20] that the dissociation of a 4-cyano-1,4-dihydropyridine is favored in a polar, highly solvating medium.[19,20]



The dissociation of the 4-cyano-1,4-dihydropyridine was not instantaneous and the rate could be measured qualitatively by a repetitive, timed determination of the ultraviolet absorption spectrum of the 4-cyano-1,4-dihydropyridine. Consequently, it was important that, for purposes of comparison, the spectra of all 4-cyano-1,4-dihydropyridines be deter-

mined at the same time after dissolution. The dissociation reaction did not occur to any noticeable extent in chloroform at 90 min. after dissolution of the sample. The spectra of 4-cyano-1,4-dihydropyridines in methanol, however, exhibited a marked decrease in the intensity of the 327-361 mμ maximum during the period between 5 min. and 60 min. after dissolution of the sample. This decrease was accompanied by the appearance of a maximum at 262-284 mμ presumably associated with the rearomatized pyridinium moiety.[20] Qualitatively, the ease of dissociation of the 4-cyano-1,4-dihydropyridine was largely dependent on the nature of the 3-substituent and was in the order $-CONH_2 > -CO_2R > -CN \sim -COCH_3 > -COPh$.

This order of substituent effects in the dissociation of 4-cyano-1,4-dihydropyridines is in agreement with the order of the σ^*_{para} constants for electron-withdrawing substituents described by Jaffe[75] who observed that the use of σ^*_{para} constants gave a "much better fit" for nucleophilic substitution reactions at an aromatic ring than other types of σ values. However, the aromatic nucleophilic substitution reactions from which the σ^* constants were obtained are of the type illustrated below, and it can be seen that these reactions are analogous to the formation and isomerization of a 6-cyano-1,6-dihydropyridine bearing an electron-withdrawing substituent at the 3-position but are not good analogs for the dissociation reactions of 4-cyano-1,4-dihydropyridines.



In fact, it is somewhat surprising that the order of the σ^*_{para} constants is in such good agreement with the order of substituent effects in the dissociation of 4-cyano-1,4-dihydropyridines since in these dissociation reactions, the electron-withdrawing substituent is ortho to the leaving group.

The nuclear magnetic resonance spectrum of a 4-cyano-1,4-dihydropyridine was better resolved than that of the corresponding pyridinium salt. Spectra were determined in deuterochloroform or dimethylsulfoxide and are given in p.p.m. relative to tetramethylsilane. The spectra of seventeen 4-cyano-1,4-dihydropyridines exhibited the following general characteristics:

a) The resonance band of the protons of the N-methyl group was found at 3.03-3.24 p.p.m. as a sharp singlet. The resonance band of the methylene protons of the N-benzyl group was found at 4.31-4.54 p.p.m. as a sharp singlet. The resonance band of the methylene protons of the N-(2,6-dichlorobenzyl) group was found at 4.54-4.83 p.p.m. as a sharp singlet.

b) The resonance band of the proton at the 2-position was found as a well defined doublet at 6.70-7.38 p.p.m. The doublet resulted from the coupling of the 2-proton with the 6-proton, J_{26}= 1.3-2.1 c.p.s. This small coupling of the 2- and 6-protons across the ring nitrogen has been reported.[21]

c) The resonance band of the proton on the 6-position was found slightly upfield from that of the 2-proton at 5.80-6.40 p.p.m. as a doublet with additional unresolved splitting, or as a quartet, sextet, or octet. The doublet resulted from coupling with the adjacent 5-proton, J_{56}= 7.4-8.8 c.p.s. In addition, a small coupling with the 2-proton was usually apparent, J_{26}= 1.3-2.1 c.p.s. Often, allylic coupling with the 4-proton was observed and increased the complexity of the splitting pattern to a sextet or octet depending on the relative magnitudes of the J_{26} and J_{46} values, J_{46}= 0.8-1.4 c.p.s.

d) The resonance band of the proton on the 5-position was found at 4.61-5.09 p.p.m. as a well defined quartet due to the previously described coupling with the adjacent 4-proton and 6-proton, J_{45}= 4.2-4.9 c.p.s., J_{56}= 7.4-8.8 c.p.s.

e) The resonance band of the proton on the 4-position was found at 4.41-4.73 p.p.m. as a doublet with additional unresolved splitting or as a well defined quartet. The doublet was a result of the previously described coupling with the 5-proton, J_{45}= 4.2-4.9 c.p.s. Quartets resulted from an additional coupling with the 6-proton, J_{46}= 0.8-1.4 c.p.s.

f) The spectra of several 3,5-disubstituted-4-cyano-1,4-dihydropyridines are also described in Table IV and the positions of the proton resonance and the coupling constants may be rationalized on the basis of the previously described facts. The assignment of signals were in good agreement in all cases with studies of the nuclear magnetic resonance spectra of dihydropyridines by other workers.[14,21,57]

Studies of the Reaction of Sodium Cyanide with Pyridinium Salts in Methanol by Ultraviolet Absorption Spectroscopy.

Charge-transfer complexes are often highly colored species and it is likely that the intensely yellow or orange solution which results from the addition of many nucleophiles to pyridinium salts[31] was one of the factors which led Kosower to propose the intermediacy of a charge-transfer complex in these reactions. These colors were not ordinarily apparent in the purified reaction products. An alternate explanation for the highly colored intermediates in such reactions may, however, be the formation of a 1,2-dihydropyridine. In fact, a dilute solution of a mixture of isomeric dihydropyridines containing a few percentage of the 1,2-dihydro isomer appears colored.

The 1,4- and 1,6-dihydropyridines prepared by the reduction of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide with sodium dithionite and sodium borohydride respectively were practically colorless. The unpurified product from the sodium borohydride reduction was intensely orange. The electronic spectrum of the unrecrystallized sample exhibited a weak maximum at 425 mμ indicating the presence of some 1,2-dihydropyridine (Part II). A single recrystallization gave a product no longer orange in color and having no absorption in the visible region of the electronic spectrum. Thus the reaction of sodium borohydride with 2 gives a small but finite attack at the 2-position; although the major product was formed by attack at the 6-position. Therefore, it is possible that the highly colored intermediates in the reactions of some nucleophiles with pyridinium ions may result from the formation of 1,2-dihydropyridines. These colored intermediates may undergo rearrangement to the corresponding 1,4-dihydropyridines or may be lost in the isolation of the major product.

In order to investigate the possible intermediacy of a 1,2- or 1,6-dihydropyridine in the reaction of sodium cyanide with pyridinium salts, the following studies were made using ultraviolet spectroscopy. A 5.0 ml. aliquot of a freshly prepared methanolic solution of the pyridinium salt (10^{-4} molar) was rapidly pipetted into 5.0 ml. of a freshly prepared methanolic solution of sodium cyanide (10^{-3} molar) in a 10.0 ml. volumetric flask. The flask was shaken vigorously for 30-45 sec. The ultraviolet-visible absorption spectrum of the solution was determined repeatedly until the spectrum ceased to change. The same procedure was repeated

in the visible absorption spectrum. (Table IX).

The results of the spectroscopic examination of the reactions of cyanide ion with all the salts of a single substituted pyridine will be considered together.

a) 3-Ethoxycarbonyl-5-bromopyridinium Salt. The methiodide (2) was the only salt of 3-ethoxycarbonyl-5-bromopyridine that was studied. A methanolic solution of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) exhibited a single maximum at 287 mμ (3.72) in the ultraviolet absorption spectrum. When a solution of 2 was treated with a solution of sodium cyanide, the initial spectrum showed absorption at 262 mμ (4.18) and 319 mμ (4.04). As the solution was allowed to stand, the 262 mμ band decreased in intensity and the 319 mμ band shifted to 343 mμ (4.04). A clean isosbestic point was observed at 329 mμ indicating that a simple equilibrium was involved.[12]

The two strong absorption maxima apparent in the initially determined spectrum can reasonably be assigned only to a 1,6-dihydropyridine. That these maxima are probably not associated with a charge-transfer complex is obvious for several reasons. First, charge-transfer complexes are not ordinarily observed at wavelengths as great as 319 mμ, in methanolic or aqueous solutions.[1] Second, the electronic transitions of charge-transfer complexes of pyridinium ions are usually seen as a single broad absorption maximum.[1] The final spectrum observed with this solution corresponded easily with that of the 1-methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28) described previously. Thus the reaction of cyanide ion with 2 produced, by a kinetically controlled process, a stable intermediate, the 1,6-dihydropyridine(47), λ_{max} = 262 and 319 mμ.

The 1,6-dihydropyridine (47) slowly underwent a conversion to a more stable product, the 1,4-dihydropyridine (28), λ_{max} = 343 mμ. This conversion was a simple process as shown by the clean isosbestic point; however, distinction between the possible routes for the rearrangement, dissociation and recombination, or an S_N2' allylic displacement of cyanide by cyanide could not be made from this evidence. The spectroscopic changes are shown in Spectrum 1 and the reactions are summarized in Figure 4.

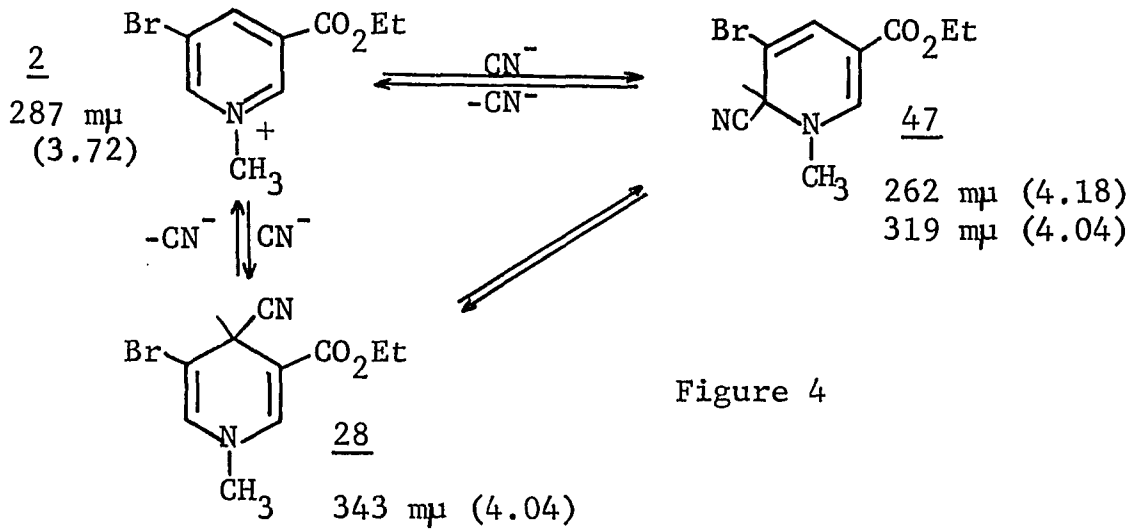
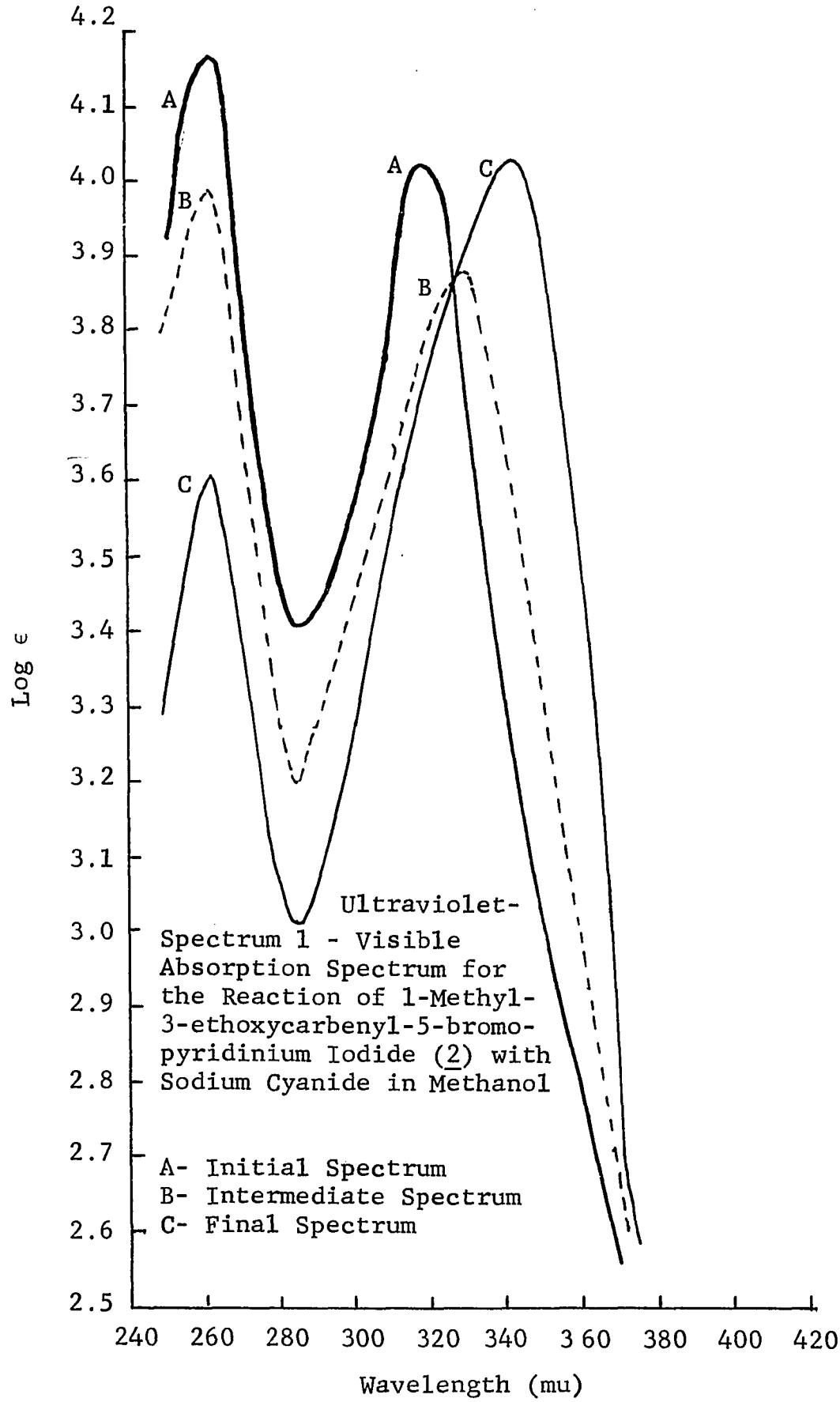


Figure 4

In order to obtain further structural evidence about the intermediate, attempts were made to isolate the compound. Concentrated aqueous solutions of cyanide ion and 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) were mixed together and a yellow oil precipitated.

Recrystallization of the crude product from alcohol gave only 1-methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28), but recrystallization of the oil from carbon tetrachloride gave a different compound. The ultra-

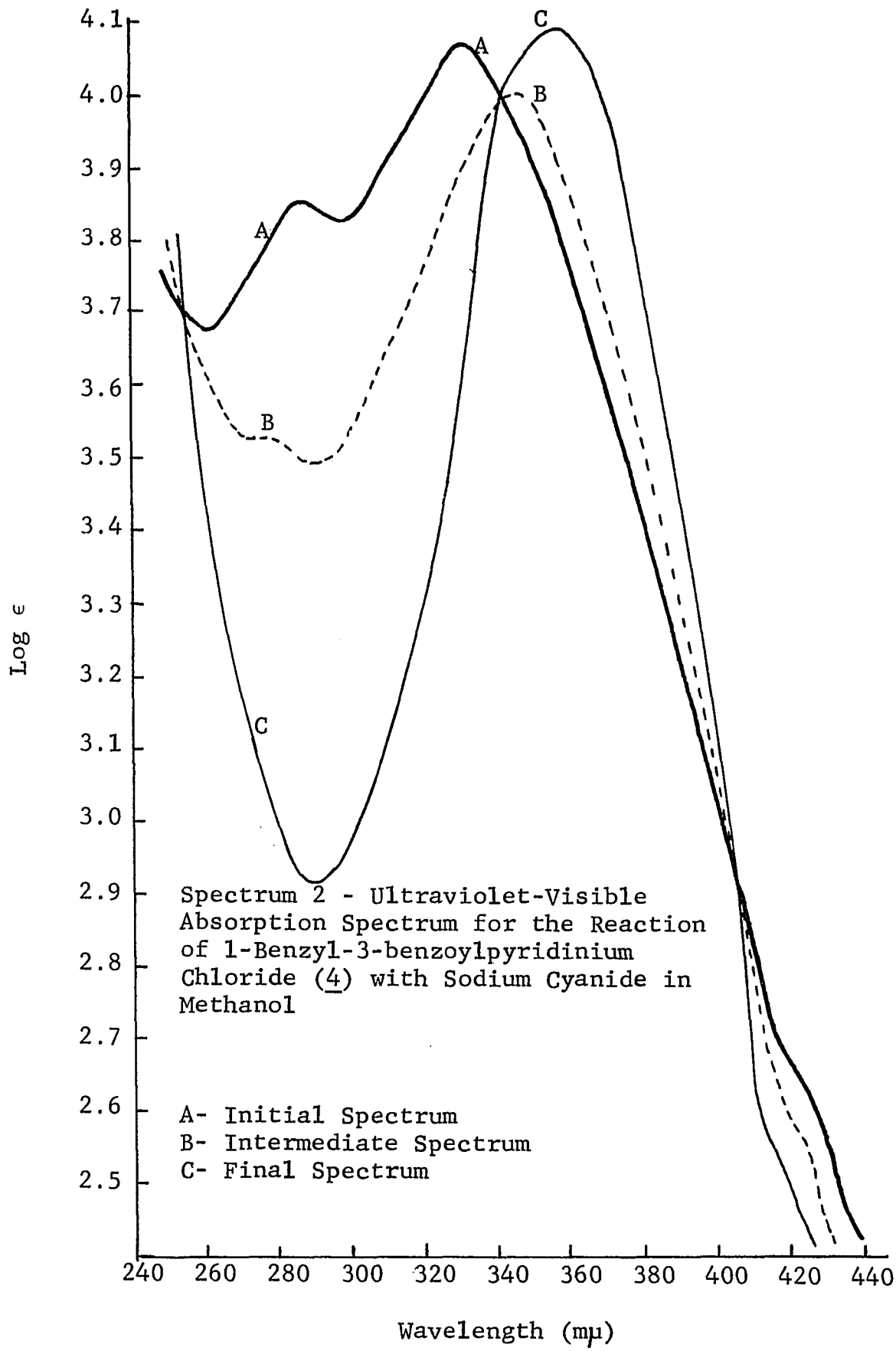


violet absorption spectrum corresponded with that of the reaction mixture of cyanide ion and 2. The nuclear magnetic resonance and infrared spectra showed that the compound was a dihydropyridine formed by cyanide addition, and the elemental analyses were consistent with this structure. All the evidence was consistent only with the structure 1-methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47). The isomerization of pure 47 in methanol was quite slow unless additional cyanide ion was added to the solution (Table XVI). Both maxima diminished in intensity upon standing with the simultaneous formation of a single maximum at 343 mμ and only weak absorption at 262 mμ. The effect of excess cyanide ion concentration on the rate of isomerization of 1-methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47) was investigated using the method described in the Experimental. These data do not allow for distinction between the two mechanisms for the rearrangement. However, correlation with the S_N2' allylic displacement is less complex since the rate increase was roughly proportional to the cyanide ion concentration.

From these studies, it is clear that the intermediate is the 6-cyano-1,6-dihydropyridine (47) and that this intermediate is capable of isomerization to a 4-cyano-1,4-dihydropyridine. That such an isomerization occurs on recrystallization explains why the products isolated from the reaction of cyanide ion with pyridinium ions have always been found to be 4-cyano-1,4-dihydropyridines. Had a stable, or reasonably stable, 6-cyano-1,6-dihydropyridine been obtained in the initial stages of the reactions, it would have certainly undergone an isomerization to the 4-cyano-1,4-dihydropyridine during the purification.

b) 3-Benzoylpyridinium Salts. Solutions of the methyl iodide (3), benzyl chloride (4), and 2,6-dichlorobenzyl chloride (5) salts of 3-benzoylpyridine were treated with solutions of sodium cyanide by the previously described method. In each reaction, the initial spectrum showed three maxima, the first at 282-286 mμ (3.86-3.97), the second at 330-332 mμ (3.99-4.20), and the third at 420-425 mμ (2.63-2.78). As the solution was allowed to stand, the first band decreased in intensity, and the second shifted to 354-359 mμ (4.04-4.15). Isosbestic points were observed at 405-415 mμ and 342-343 mμ. The final electronic spectra corresponded to those of the corresponding 4-cyano-1,4-dihydropyridines 29, 30, and 31, and showed only a single maximum at 355-361 mμ (4.10-4.16). The explanation of these data is based on the same considerations as for the reaction of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) with sodium cyanide. These data show clearly that the kinetically controlled reactions of cyanide ion with 3-benzoylpyridinium ions produces the 1,2- and 1,6-dihydropyridines and that these undergo rearrangement to the 1,4-dihydropyridine on standing. See Figure 5 and Spectrum 2 for these results.

The behavior of the long wavelength maximum depended on the nature of the N-substituent. Qualitatively, the larger the N-substituent, the more rapidly the 420-425 mμ absorption maximum diminished. This, presumably, was a result of an unfavorable steric interaction between the larger N-substituent and the 2-cyano group of the 2-cyano-1,2-dihydropyridine isomer responsible for the long wavelength absorption.



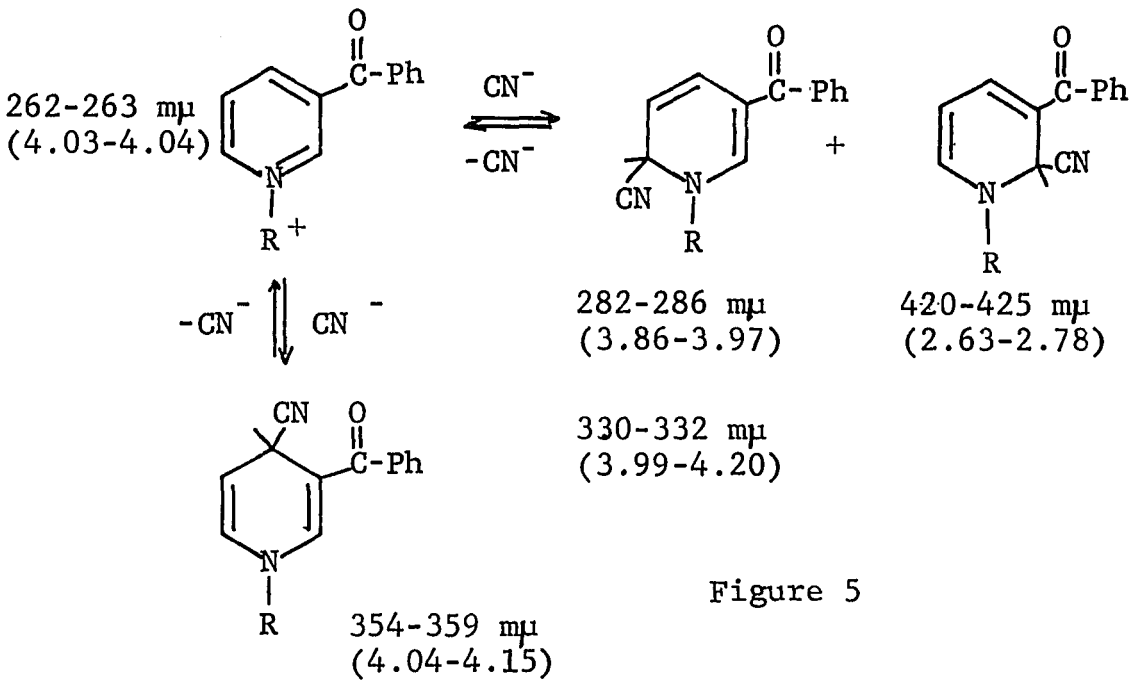
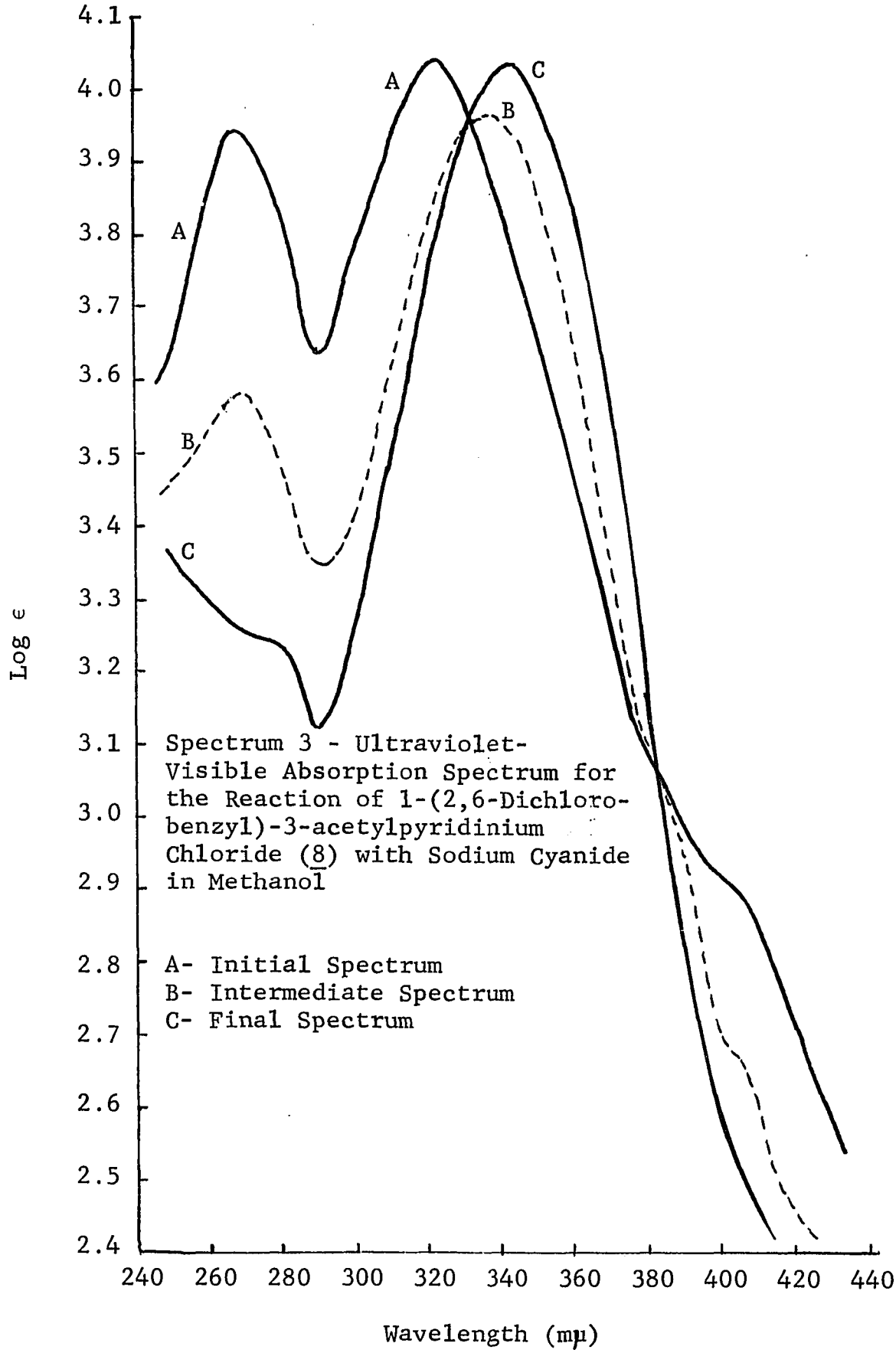


Figure 5

c) 3-Acetylpyridinium Salts. Methanolic solutions of the methyl iodide (6), benzyl chloride (7), and 2,6-dichlorobenzyl chloride (8) salts of 3-acetylpyridine were treated with solutions of sodium cyanide by the previously described method. The spectroscopic changes during the course of the reaction corresponded to those of the analogous 3-benzylpyridinium salts though the λ_{max} and log ϵ values of the absorption maxima were different from those of the 3-benzoylpyridinium salts. The rate of decrease in the intensity of the absorption maxima at 269-270 mμ and 405-410 mμ appeared to be slightly faster than those of the corresponding 3-benzoylpyridinium salts. This was interpreted as a result of a poorer stabilization of the 1,2- and 1,6-dihydropyridine isomers by the acetyl group compared to the benzoyl group. The final spectra in the reactions of the 3-acetylpyridinium ions corresponded to the spectra of the pure 4-cyano-1,4-dihydropyridines 32, 33, and 34.



d) 3-Cyanopyridinium Salts. Methanolic solutions of the methyl iodide (9), benzyl chloride (10), and 2,6-dichlorobenzyl chloride (11) salts of 3-cyanopyridine were treated with solutions of sodium cyanide by the previously described method. In each reaction, the initial spectrum showed three important maxima, the first at 245-253 mμ (3.52-3.84), the second at 303-312 mμ (3.73-3.88), and the third at 370-372 mμ (3.11-3.24). The maxima at 245-253 mμ and 303-312 mμ changed, as the solutions were allowed to stand, in a manner similar to that described for the 3-benzoylpyridinium salts. In every reaction, however, the maxima at 245-253 mμ and 370-372 mμ decreased in intensity more slowly than the corresponding maxima in the reactions of the 3-acetylpyridinium ions. This was presumably a result of the higher electrophilicity of the 3-cyanopyridinium ion as compared with the 3-acetylpyridinium ions, and of the increased stabilization of the 1,2- and 1,6-dihydro-isomers by the stronger electron-withdrawing 3-cyano substituent compared to the acetyl group. This effect would be predicted on the basis of the higher σ^{*}_{para} constant of the cyano group compared to the acetyl group.[75] The final spectrum of each reaction was dominated by a single maximum in the region 324-331 mμ (3.76-3.86) although weak absorption remained below 268 mμ (Table IX). Isosbestic points were observed at 318-319 mμ and 354-360 mμ in all three reactions. The final spectra corresponded to those exhibited by the pure 4-cyano-1,4-dihydropyridines 35, 36, 37. These data again show that the initial reaction of cyanide ion is with the 2- and 6-positions of the 3-cyanopyridinium ion. The 1,2- and 1,6-dihydropyridines thus formed are converted to the more stable 1,4-dihydropyridine in an equilibrium process. These reactions are summarized in Figure 6.

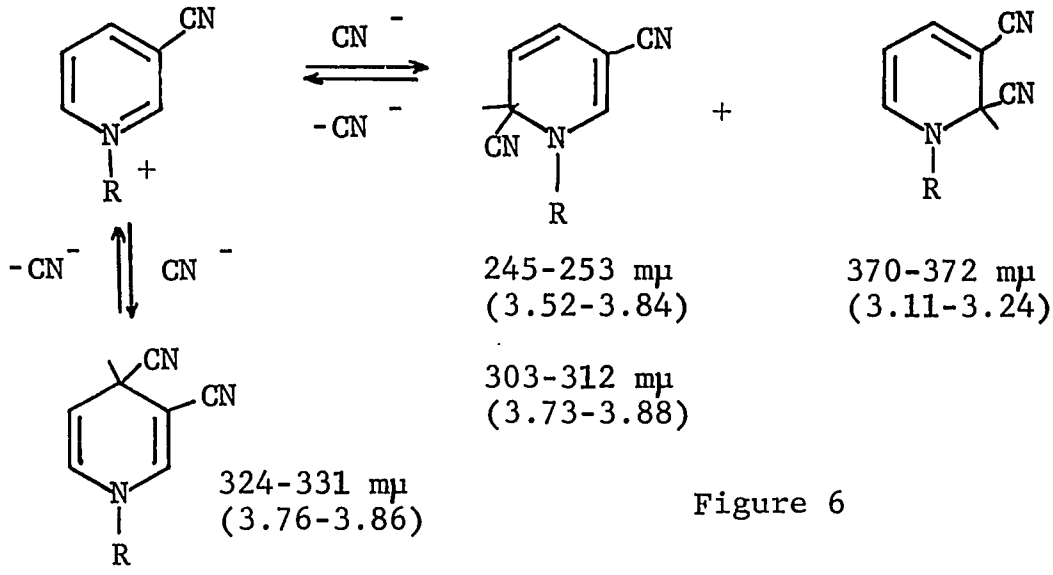
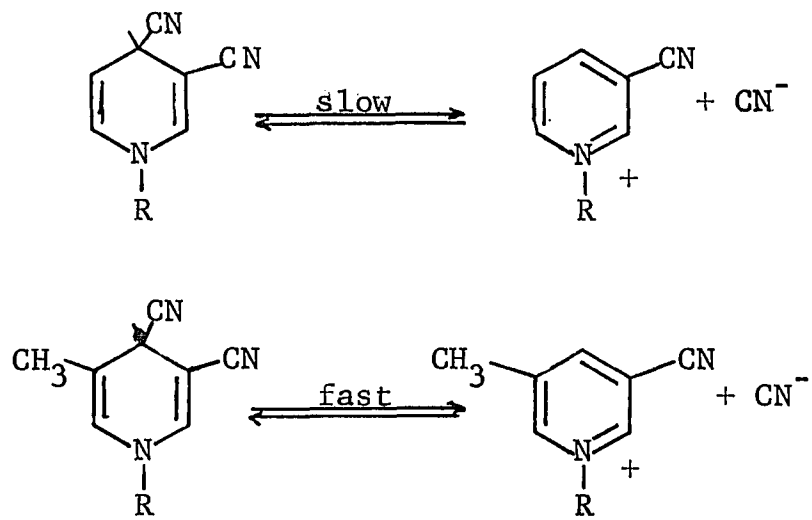


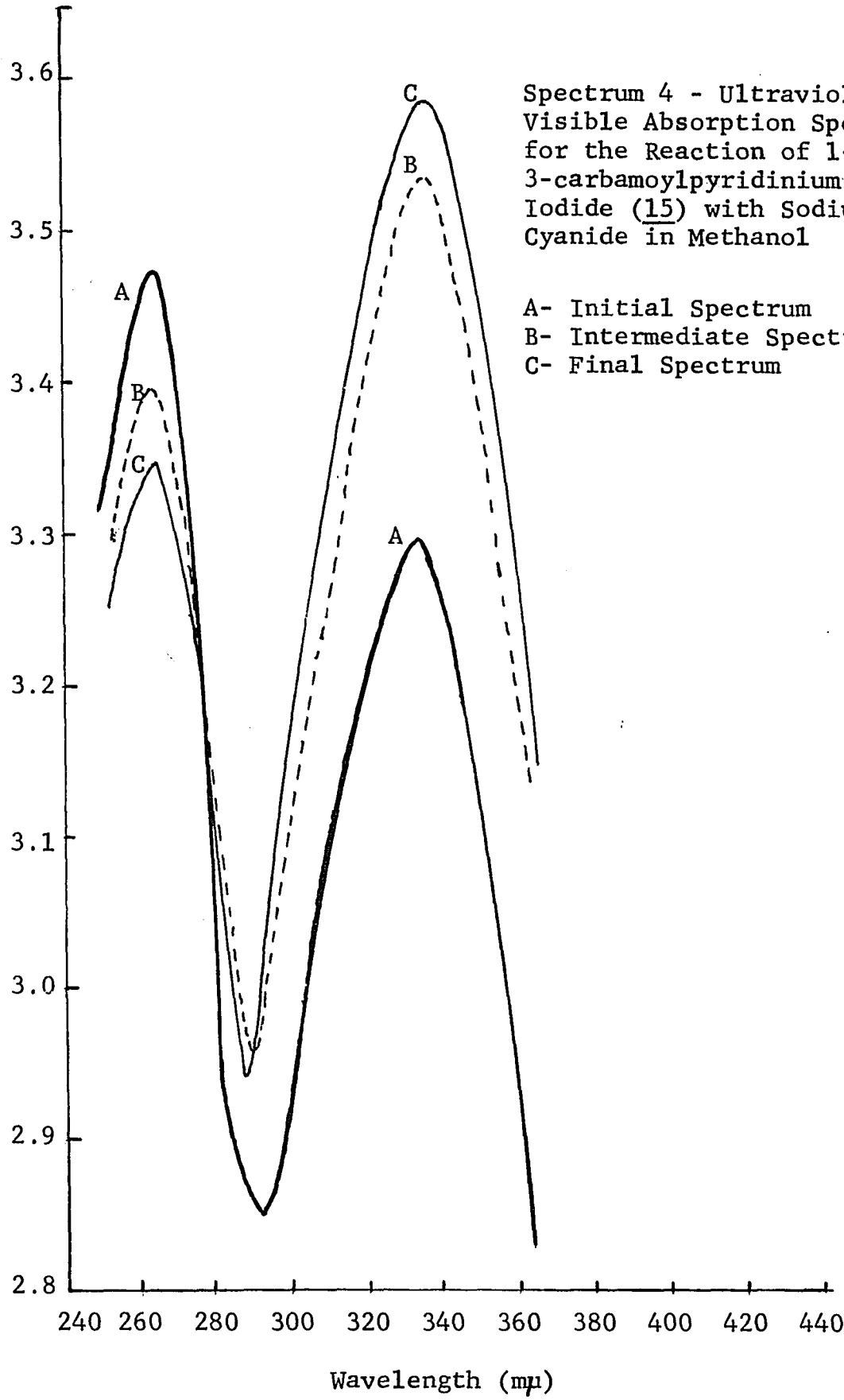
Figure 6

e) 3-Cyano-5-methylpyridinium Salts. The reactions of the methyl iodide (12), benzyl bromide (13), 2,6-dichlorobenzyl chloride (14) salts of 3-cyano-5-methylpyridine with sodium cyanide appeared anomalous when compared with similar reactions of the corresponding 3-benzoyl-, 3-acetyl-, and 3-cyanopyridinium salts. Initially the reaction mixtures containing 12, 13 and 14 showed a single maximum at 313-323 mμ (3.80-3.94) with absorption having no maximum in the 250-280 mμ region. This maximum shifted very rapidly to a single, well-defined peak in the 325-332 mμ region (Table IX). The final spectra of the reaction mixtures corresponded to the spectra exhibited by the pure 4-cyano-1,4-dihydropyridines 38, 39, and 40. The long wavelength maximum observed in each of the reactions with the 3-cyanopyridinium salts was not evident with salts 12, 13, and 14, nor was a well-defined maximum in the 250-280 mμ region, expected of a 6-cyano-1,6-dihydropyridine, present. The absorption at 250-280 mμ decreased in intensity as the solution was allowed to stand. Clean isosbestic points were observed at 321-322 mμ in all three reactions, however.

A comparison of these data with the observations with 3-benzoyl-, 3-acetyl-, and 3-cyanopyridinium salts suggested that again the kinetically favored reaction of the cyanide was with the 2- and 6-positions of 12, 13, and 14; however, the rate of reactions at the 4-position, and thus the rearrangement of the 1,2- and 1,6-dihydropyridines was more rapid than with the salts 9, 10, and 11. The closeness of the rates of reaction of cyanide ion at the 4- and 6-positions probably results from a decrease in the rate of reaction at the 6-position due to decreased electrophilicity of the 3-cyano-5-methylpyridinium ion as compared with the corresponding 3-cyanopyridinium ion. The observation that ring-methyl groups decrease the electrophilicity of the pyridinium ring has been reported,[1] and this would be expected from the known hyperconjugative and inductive effects of alkyl groups.[6] A further indication that the 5-methyl substituent decreased the electrophilicity of the pyridinium ring was apparent from the observation that the dissociations of the 3,4-dicyano-1,4-dihydropyridines were much more rapid and were greater for the 5-methyl isomers than for the 5-hydrogen isomers (Table VI).



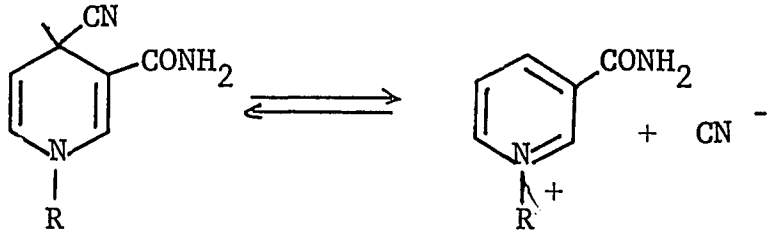
f) 3-Carbamoylpyridinium Salts. The nicotinamide adenine dinucleotide (NAD) model compounds consisting of the methyl iodide (15), benzyl chloride (16), and 2,6-dichlorobenzyl chloride (17) salts of 3-carbamoylpyridine (nicotinamide) gave the most confusing results of those from any pyridinium salt studied. The ultraviolet absorption spectra of the 3-carbamoylpyridinium salts 15, 16, and 17 exhibited a single maximum at 264-267 mμ (3.61-3.66). The spectral changes of their reactions with cyanide ion generally resembled those of the same reactions involving 3-cyano-5-methylpyridinium salts. The reactions reached completion very rapidly, and no well-defined absorption bands characteristic of the 1,2-dihydro- or 1,6-dihydropyridine isomers were observed. By inference from the previously described results, it seems most reasonable to propose that the reaction involved attack at the 6- (and 2-) position followed by a very rapid isomerization yielding the 3-carbamoyl-4-cyano-1,4-dihydropyridines 41, 42, and 43. The reaction of 1-methyl-3-carbamoylpyridinium iodide (15) with cyanide ion appeared different from the reactions of the corresponding benzyl chloride (16) and 2,6-dichlorobenzyl chloride (17) salts with cyanide ion. The ultraviolet absorption spectrum of the reaction of 15 with cyanide ion is illustrated in Spectrum 4. Even in a solution containing a ten-fold excess of sodium cyanide, much of the pyridinium salt (15) remained apparently unreacted although the ultraviolet absorption spectrum of the reactions of 16 and 17 with cyanide ion indicated no unreacted pyridinium salt.



Spectrum 4 - Ultraviolet-Visible Absorption Spectrum for the Reaction of 1-Methyl-3-carbamoylpyridinium Iodide (15) with Sodium Cyanide in Methanol

A- Initial Spectrum
B- Intermediate Spectrum
C- Final Spectrum

Chloroform solutions of the pure 4-cyano-1,4-dihydropyridines 41, 42, and 43 derived from 15, 16, and 17 respectively exhibited a single, stable ultraviolet absorption maximum at 334-338 mμ (3.67-3.85). These 4-cyano-1,4-dihydropyridines dissociated readily in methanol, however (Table VI). The initially determined spectra of 41, 42, and 43 in methanol exhibited two maxima, the first at 263-273 mμ (3.27-3.42), and the second at 331-337 mμ (3.53-3.79). As the solutions were allowed to stand, the first maximum increased in intensity log ε = 3.50-3.62, and the longer wavelength maximum decreased in intensity to log ε = 2.70-3.39. Presumably, these changes resulted from the dissociation reaction illustrated below.



g) Reaction of Other Quaternary Salts with Sodium Cyanide. The reactions of pyridinium ions having no electron-withdrawing substituents on the 3-position were also used to investigate factors influencing the nucleophilic attack of cyanide on pyridinium ions.

Methanolic solutions of 1,2-dimethylpyridinium iodide (21) and 1,4-dimethylpyridinium iodide (22) exhibited maxima at 265 mμ (3.76) and 256 mμ (3.60) respectively (Table X). The spectra of these compounds remained unchanged in the presence of a ten-fold excess of sodium cyanide. The ultra-

violet spectrum of a solution of 1-methyl-4-methoxycarbonyl-pyridinium iodide (24) also remained unchanged in the presence of a ten-fold excess of sodium cyanide. As a solution of 24 and sodium cyanide was allowed to stand, the maximum at 275 mμ (3.63) characteristic of 24 decreased slowly in intensity and shifted slightly to shorter wavelengths, presumably as a result of the base-catalyzed hydrolysis of the 4-methoxycarbonyl group by the small amount of water in methanol. Such reactions have been described previously.[30]

The spectrum of a methanolic solution of 1-methyl-3,5-diphenylpyridinium iodide (23) remained unaffected by a hundred-fold excess of sodium cyanide. Since 23 was known to undergo reduction with sodium borohydride or dithionite ion,[14] the lack of reactivity with cyanide ion could not be explained on steric grounds. Its non-reactivity with cyanide may be a result of the relatively low electrophilicity of 23 compared with pyridinium ions having a strong electron-withdrawing substituent at the 3-position. Thus, 23 reacts with strong nucleophiles such as hydride ion and the phenyl substituents stabilize the dihydropyridine that is formed. With weaker nucleophiles such as cyanide ion, 23 is not sufficiently electrophilic to give an initial reaction.

Significantly, studies of the ultraviolet absorption spectrum of the reactions of sodium cyanide with methanolic solutions of 1-methyl-2-benzoylpyridinium iodide (19) and 1-methyl-4-benzoylpyridinium iodide (20) indicated that 19 and 20 were also unaffected by a ten-fold excess of sodium

cyanide. Their apparent unreactivity is probably due to the instability of the product which would be formed by addition of cyanide ion to the pyridinium ion.

The reaction of 1-methylquinolinium iodide (25) with sodium cyanide in methanol gave no indication of any 2-cyano-1, 2-dihydroquinoline intermediate (Table XI). The final ultraviolet absorption spectrum of the reaction mixture exhibited only a single maximum at 299 mμ (4.07) associated with a 4-cyano-1, 4-dihydroquinoline of the type described by Kaufmann.[47]

The spectroscopic changes associated with the reaction of 1-benzylquinolinium bromide (26) with sodium cyanide generally resembled those for 25. The initial spectrum, however, indicated an additional weak absorption at 341 mμ (3.19) which decreased in intensity as the solution was allowed to stand. This long wavelength absorption maximum may be a result from 1-benzyl-2-cyano-1,2-dihydroquinoline, for an analogous compound 1,2-dimethyl-1,2-dihydroquinoline[66] exhibited absorption maxima at 234 mμ (4.3), 285 mμ (3.3), and 355 mμ (3.4). If the 2-cyano-1,2-dihydroquinoline was an intermediate, it underwent rearrangement to the corresponding 1,4-dihydroquinoline for the final spectrum of the reaction mixture showed only a single maximum at 299 mμ (3.95).

The changes in the ultraviolet absorption spectrum associated with the reaction of 1-methyl-2-phenylquinolinium iodide (27) with sodium cyanide in methanol are described in Table XI. The long wavelength maximum at 378 mμ (3.00) which slowly appeared as the solution was allowed to stand may be associated with a 2-cyano-1,2-dihydroquinoline since a model compound 1-methyl-2-phenyl-1,2-dihydroquinoline[67]

exhibited a long wavelength maximum at 362 mμ (3.4).

The reactions of 25, 26, and 27 were not good models for the comparison of the nucleophilic addition of cyanide ion and quinolinium ions. Studies of the reactions of cyanide ion with quinolinium compounds substituted at the 3-position with electron withdrawing groups would probably provide more satisfactory evidence concerning the possible formation of a 2-cyano-1,2-dihydroquinoline as an intermediate.

The Isolation and Characterization of the Intermediate 6-Cyano-1,6-dihydropyridines

An examination of the reaction of several pyridinium salts with sodium cyanide under irreversible conditions confirmed the conclusions derived from the ultraviolet absorption studies of the reactions run under reversible conditions. The irreversible conditions for the cyanide reaction were achieved by using water as the solvent, thus causing precipitation of the non-ionic intermediates. The addition of a concentrated aqueous solution of the pyridinium ion to a concentrated aqueous solution of sodium cyanide caused the precipitation of a yellow or orange oil, as anticipated from the very low solubility of most dihydropyridines in water. Dissolution of the oily material in methanol or ethanol resulted in a crystalline product characterized in each case as a 4-cyano-1,4-dihydropyridine. The characterization of the intermediate species was made difficult by the fact that dissolution of oils in most solvents allowed the isomerization of the 6-cyano-1,6-dihydropyridine to the 4-cyano-1,4-dihydropyridine to occur

and in most cases, the 6-cyano-1,6-dihydropyridine could not be isolated in a stable, crystalline form.

The dissolution of the yellow oil (2*) from the reaction of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) with cyanide ion in carbon tetrachloride and fractional evaporation of the solution permitted the isolation of a stable, crystalline compound which was characterized as a 6-cyano-1,6-dihydropyridine (47) on the basis of its microanalytical data, ultraviolet absorption spectrum (vide supra), and nuclear magnetic resonance spectrum as described below.

Studies of the Isomerization of 6-Cyano-1,6-dihydropyridines Using Nuclear Magnetic Resonance Spectroscopy

The three pyridinium salts used for these studies were 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2), 1-benzyl-3-benzoylpyridinium chloride (4), and 1-benzyl-3-cyanopyridinium chloride (10).

The reaction of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) with sodium cyanide gave a yellow oil (2*). The initially determined nuclear magnetic resonance spectrum of a solution of 2* in deuterochloroform indicated that two species were present in the solution. As the solution was allowed to stand, a very rapid isomerization occurred as indicated in the middle and bottom spectra of Spectrum 7. The final spectrum was identical with that of 1-methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28) and showed none of the other isomer. The assignment of the bands in the spectrum of 28 was made by a comparison with the signals of the model compound 1-methyl-3-ethoxycarbonyl-4-bromo-1,4-dihydropyridine[14] (46). The resonance band of

the 4-proton of 28 was found at much lower field than the resonance band of the protons on the 4-position of 46 as could be predicted from the known deshielding properties of the cyano group.[8] Only small amounts of 28 were observed in the initially determined spectrum. The structural assignment of the initially formed species (2*) in the reaction was made by comparing its nuclear magnetic resonance spectrum with that of 1-methyl-3-ethoxycarbonyl-5-bromo-1,6-dihydropyridine[14] (48). The resonance band of the 6-proton of 2* was found at much lower field than that of the 6-protons of 48. The nuclear magnetic resonance spectrum of the crystalline product (47) obtained by dissolution of 2* in carbon tetrachloride followed by fractional crystallization of the solution was identical with that of 2* and thus 47 was characterized as 1-methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine.

Interestingly, a concentrated solution of 2* in warm carbon tetrachloride showed no noticeable equilibration in the nuclear magnetic resonance spectrum after standing for 30 min. This apparently reflected the inability of carbon tetrachloride to accommodate the ionic species presumably involved in the rearrangement of the 6-cyano-1,6-dihydropyridine to the 4-cyano-1,4-dihydropyridine. Since the 6-cyano-1,6-dihydropyridine (47) did not isomerize to the 4-cyano-1,4-dihydropyridine (28) in carbon tetrachloride, fractional crystallization of the material in the carbon tetrachloride solution provided pure 1-methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47) as described in the Experimental.

The infrared spectra of 28 and 47 are illustrated in Spectrum 5 and Spectrum 6, and each compound was found to exhibit strong absorption at wavelengths at which the other did not. Thus, infrared spectroscopy provided a simple method for estimating the 1,4/1,6-dihydropyridine ratio in the several fractions of crystalline material which resulted from evaporation of a carbon tetrachloride solution of 2*. Table XIII describes the infrared spectra of pure samples of 28 and 47 and of a 50-50 mixture of 28 and 47.

Similar studies of the reactions of 4 and 10 with cyanide ion gave results analogous to those for the reaction of 2 with cyanide ion. However, it was not possible to inhibit the isomerization of the initially formed species in these reactions or to isolate a stable, crystalline 6-cyano-1,6-dihydropyridine adduct of either 4 or 10 because the oil from the initial reaction with cyanide ion was not sufficiently soluble in carbon tetrachloride.

The reaction of 1-benzyl-3-cyanopyridinium chloride (10) with sodium cyanide also gave a yellow oil whose nuclear magnetic resonance signals were attributed to 1-benzyl-3,6-dicyano-1,6-dihydropyridine (49). The signals of 49 decayed rapidly with the simultaneous formation of new signals which were shown to be identical with those of pure 1-benzyl-3,4-dicyano-1,4-dihydropyridine (36)(Table V). The structural assignment of the initially formed species in the reaction was made by a comparison of its nuclear magnetic resonance spectrum with that of 1-benzyl-3-carbamoyl-1,6-dihydropyridine[21] (90) and 1-benzyl-3-cyano-6-phenyl-1,6-dihydropyridine[76] (91) derived from the sodium borohydride and Grignard reactions of the corresponding pyridinium salts. The assignment of the signals of the NCH_2Ph group were made

by a comparison with the signals of the NCH_2Ph groups of the numerous dihydropyridines listed in Table VII. The signal found furthest downfield in the spectra of the model compounds was assigned to the 2-proton as a result of its proximity to the deshielding 3-substituent and ring nitrogen.[21,76] The resonance band of the 4-proton was found at 0.95-1.08 p.p.m. upfield from that of the 2-proton as a quartet with additional unresolved splitting. The assignment of the signal of the 5-proton was quite simple since the 10-12 c.p.s. coupling apparent in the spectra of 90 and 91 could be reasonably assigned only to the interaction of the vicinal 4- and 5-protons. The magnitude of the J_{56} value in the spectra of 90 and 91 was found to be about half of that of the J_{45} value. Thus, the remaining unassigned signal found furthest upfield with a coupling constant of about 4 c.p.s. was assigned to the 6-proton. The position of the proton resonance for each of the protons in the initially formed species from the reaction of 10 with cyanide ion corresponded closely with those for the model compounds, and the magnitude of the coupling constants for the protons of the initially formed species confirmed that it was 1-benzyl-3,6-dicyano-1,6-dihydropyridine (49). The reader is referred to the excellent discussion by Wallenfels[21] on the general characteristics of the nuclear magnetic resonance spectra of 1,2-, 1,4-, and 1,6-dihydropyridines.

The reaction of 1-benzyl-3-benzoylpyridinium chloride (4) with sodium cyanide gave a yellow oil whose nuclear magnetic resonance signals showed it to be 1-benzyl-3-benzoyl-6-cyano-1,6-dihydropyridine (50) (Table XII). The signals of 50 decayed rapidly with the simultaneous formation of new signals which were shown to be identical with those of pure 1-benzyl-3-benzoyl-4-cyano-1,4-dihydropyridine (30).

The assignment of the signals of the initially formed species was made complex because the initially determined spectrum of the oil showed large amounts of the 4-cyano-1,4-dihydropyridine isomer to be present. Furthermore, the signals of several of the ring protons of the initially formed species were superimposed on the signals of the 4-cyano-1,4-dihydropyridine (30). For these reasons, a determination of the splitting patterns of the signals of 50 could not be made with accuracy. However, the positions of the signals of the initially formed species could be determined with a fair degree of accuracy and these are given in Table XII. The signal furthest downfield was assigned to the 2-proton by analogy with the results from 49, 90, and 91. The signal found upfield from that of the 2-proton was assigned to the 4-proton for similar reasons. It is interesting to compare the large downfield shift of the signals of the 2- and 4-protons of 50 with the moderate downfield shift of the 2- and 4-protons of 49, 90, and 91. In the nuclear magnetic resonance spectra of the corresponding pyridinium salts, for example, the resonance bands of the 2- and 4-protons of the 3-benzoylpyridinium salts are found at slightly higher fields relative to the 2- and 4-protons of other 3-carbonylpyridinium salts (vide supra). Apparently, for 1,6-dihydropyridines, the 3-benzoyl substituent must lie within the plane of the dihydropyridine ring in order that the strong deshielding effect of the 3-benzoyl group may be experienced by the 2- and 4-protons. The assignments of the remaining complex signals were made on the basis of the large coupling constant exhibited by the signal at 5.25 p.p.m. and the smaller coupling constant of the signal at 5.16 p.p.m. For the reasons described in the structure determination of 49, the larger coupling must result from the interaction of

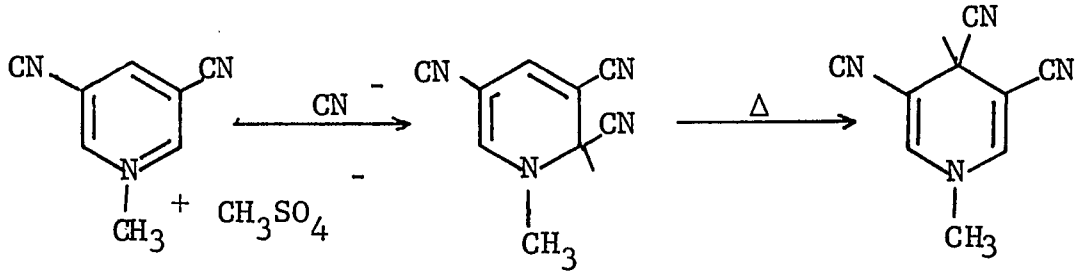
the 4- and 5-protons and thus the signal at 5.25 p.p.m. must be assigned to the 5-proton.

These results support the evidence and conclusions derived from ultraviolet absorption studies of the reactions of cyanide ion and pyridinium ions. The initial product formed in these reactions has been shown to be a 6-cyano-1,6-dihydropyridine. This isomer is thermodynamically unstable relative to the 4-cyano-1,4-dihydropyridine which results if a solution of the 6-cyano-1,6-dihydropyridine is allowed to stand under reversible conditions.

Independent evidence describing the formation of stable 6-cyano-1,6-dihydropyridines in the reaction of substituted pyridinium ions with cyanide ion has recently been reported by Wallenfels.[22,23] His earlier papers had reported that the anion affinity of pyridinium salts was strongly influenced by the introduction of electron-withdrawing substituents at the 3- and 5-positions of the ring.[19,20]

The pyridinium ring of 1-methyl-3,5-dicyanopyridinium methylsulfate (58) was expected to be strongly electrophilic because of the effects of the positive charge of the pyridinium ion, and the effects of two strongly electron-withdrawing substituents. The reaction of an aqueous solution of 1-methyl-3,5-dicyanopyridinium methylsulfate (58) with an aqueous solution of potassium cyanide gave, after 30 min., a 72% yield of a crystalline product identified as 1-methyl-2,3,5-tricyano-1,2-dihydropyridine (59) by its elemental analysis and by its ultraviolet absorption spectrum λ_{max}^{MeOH} ($\log \epsilon$)= 246 mμ (3.92) and 350 (3.95).[22] Wallenfels later reported that a methylene chloride solution of 59 exhibited absorption maxima at 245 mμ (ϵ =4100) and 377 mμ (ϵ =5700).[23]

A small amount of 1-methyl-3,4,5-tricyano-1,4-dihydropyridine (60) was also isolated. The high degree of stability of 59 was indicated by the fact that its isomerization to 60 could be accomplished only by warming a melt of 59 at 125° for a short time or by heating a dimethylformamide solution of 59 at 150-160°. Compound 60 exhibited a single maximum in the ultraviolet absorption spectrum λ_{max}^{MeOH} ($\log \epsilon$)= 359 (3.87).

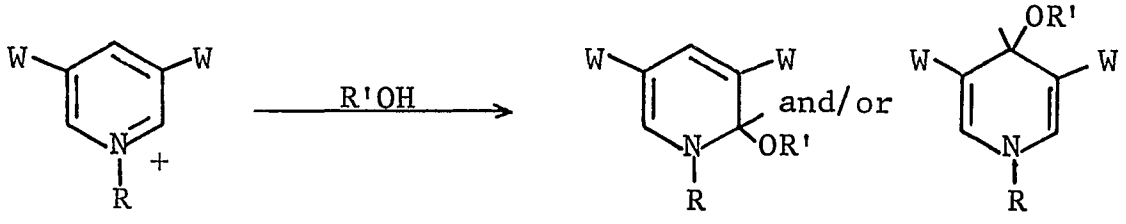


58 59 60

From these considerations, it appears that the preferential formation of 4-cyano-1,4-dihydropyridines may be explained in terms other than those involving the intermediacy of a "charge-transfer" complex. The ratio of the products from reversible reactions depends on the relative thermodynamic stabilities of the possible products, and the previously described work has shown that the reactions of cyanide and pyridinium ions are reversible under certain conditions. The 6- (2-) cyano-1,6- (-1,2-) dihydropyridine is formed as a result of a kinetically controlled addition process, and since 4-cyano-1,4-dihydropyridines are the ultimate products of these reactions, it must follow that the thermodynamics of the equilibrium favor the 4-cyano-1,4-dihydropyridine isomer.[13] The kinetically controlled reaction of cyanide with pyridinium ions appears to be

influenced by the same steric and electronic factors involved in similar reactions involving other nucleophiles.

It was interesting to compare the ultraviolet absorption spectra of the 3,5-symmetrically disubstituted pyridinium ions. It was observed that methanolic solutions of pyridinium salts with strongly electron-withdrawing groups such as cyano and methoxycarbonyl at the 3- and 5-positions exhibited strong absorption maxima above 300 mμ while the 3,5-dicarbamoylpyridinium salt did not. This long wavelength absorption maximum apparently results from the dihydropyridine(s) formed from the addition of the elements of a solvent anion to the 2- or 4- position of the pyridinium salts containing the strongly electron-withdrawing substituents. This is illustrated below where W= electron-withdrawing substituent.



This observation was implicit in a private communication with Wallenfels[23] in which he reported the ultraviolet absorption spectrum of 1-methyl-3,5-dicyanopyridinium methylsulfate (58) as a single maximum at 279 mμ in an aqueous solution of pH< 1.8. This solvent is an unusual one for the determination of the spectrum of a pyridinium salt and was presumably used in order to inhibit the reaction illustrated above.

The fact that certain nucleophiles form 1,4-dihydropyridines on reaction with pyridinium ions has been rationalized on the basis of the orientation of the reacting ions in a "charge-transfer" complex. It seems clear that a better explanation may be available. Where reversible addition of a nucleophile can be demonstrated, one would anticipate the final product being the isomer of lowest free energy. With cyanide adducts this has been shown to be the 1,4-dihydro isomer and probably can be generalized to say that with analogous 1,2-, and 1,4, and 1,6-dihydropyridines, the 1,4-dihydropyridine will have the lowest free energy. Thus any nucleophilic addition carried out under equilibrium condition should lead ultimatily to the 1,4-dihydro isomer.

SUMMARY

The following is a summary of the important results and conclusions from these studies.

a) The strength of the electron-withdrawing substituents on pyridinium ions is of primary importance in determining whether 1,2-dihydro- and 1,6-dihydropyridines can be observed during the reaction of pyridinium ions with cyanide ions. The possibility of observing 1,2- or 1,6-dihydropyridines in these reactions increases with the electron-withdrawing power of the substituent(s).

b) The stability of the 1,2-dihydro- or 1,6-dihydropyridines increases with the electron-withdrawing power of the substituent(s).

c) The stability of the 2-cyano-1,2-dihydropyridine is sensitive to the size of the N-substituent. The 2-cyano-1,2-dihydropyridines isomerize more rapidly as the size of the N-substituent increases, presumably as a result of unfavorable steric interactions.

d) Hyperconjugative electron release by methyl substituents on the pyridinium ring causes a marked decrease in the electrophilicity of the pyridinium ring and in the possibility of observing relatively stable 2-cyano-1,2-dihydro- or 6-cyano-1,6-dihydropyridines in the in situ reactions.

e) The presence of an electron-withdrawing substituent on a pyridinium ion is not, in itself, sufficient to cause the ring to be susceptible to attack by cyanide ion. The substituent must be in a position to both decrease the

electron density at the 2-, 4-, and 6-positions and render these positions susceptible to attack, and to stabilize the dihydropyridine resulting from the addition of a cyanide ion to the pyridinium ion.

EXPERIMENTAL

General

Melting Points. Part I. Melting points were determined using a Hoover capillary melting point apparatus and are corrected.

Melting Points. Part II. Melting points were determined using a Kofler hot-stage melting point apparatus equipped with a polarizing microscope and are uncorrected.

Ultraviolet Absorption Spectra. The ultraviolet absorption spectra were determined using a Perkin-Elmer Model 4000 recording spectrophotometer. The spectra were determined in the solvents indicated. Wavelengths are given in millimicrons, mμ, and absorption is reported as the logarithm of the molar absorbance (molecular extinction coefficients) ϵ .

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using a Varian Model A-60 proton magnetic resonance spectrometer. The spectra were determined in the solvents indicated, and the chemical shifts are given in p.p.m. relative to tetramethylsilane (TMS) as an internal standard or in p.p.m. relative to DOH at δ = 4.75 p.p.m. (relative to tetramethylsilane).

Infrared Absorption Spectra. The infrared absorption spectra were determined using a Perkin-Elmer Model 21 infrared spectrophotometer (-21), a Perkin-Elmer Infracord spectrophotometer (-In), and a Perkin-Elmer Model 337 infrared spectrophotometer (-33). The position of the

absorption bands is given in wave numbers, $cm.^{-1}$. The spectra of liquids were determined as films, and the spectra of solids were determined as mulls in Halocarbon oil from 4000 $cm.^{-1}$ to 1300 $cm.^{-1}$, and in Nujol from 1300 $cm.^{-1}$ to 650 $cm.^{-1}$. Halocarbon oil was from Halocarbon Products Corp., Hackensack, N. J. and Nujol from Plough, Inc., San Francisco, Calif.

Analytical Data. Microanalyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. (Sch), by Drs. Weiler and Strauss, Oxford, England (W&S), and in these laboratories using an F & M Model 180 carbon, hydrogen, and nitrogen analyzer (F&M).

Solvents. Solvents used in spectroscopic studies were usually Spectranalyzed grade from Fisher Scientific Company, Fair Lawn, N. J.

Methods of Preparation of Quaternary Salts. Quaternary salts were prepared by one of the following four methods.

(a) Methiodides. A solution of methyl iodide and the substituted pyridine in a 1.5:1 molar ratio in acetone was heated for 2-24 hr. The solution was cooled in an ice bath. The solid precipitate was separated by filtration and recrystallized from acetone or isopropyl alcohol.

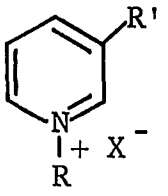
(b) Benzyl Bromides or Chlorides. Equimolar amounts of the pyridine and benzyl halide were heated under reflux in acetone or isopropyl alcohol with a trace of sodium iodide until a solid precipitate was obtained. The mixture was cooled in an ice bath, the solid product was separated by filtration, and was recrystallized from acetone or isopropyl alcohol.

(c) 2,6-Dichlorobenzyl Chlorides. Equimolar amounts of the pyridine and 2,6-dichlorobenzyl chloride were heated in anhydrous methanol under reflux for three days. The solvent was evaporated under reduced pressure and the residue was triturated with 100 ml. of ether. The solid which formed was separated by filtration, washed with 200 ml. of ether, and triturated with hot acetone. This procedure gave products of satisfactory purity.

(d) If neither method (a) nor (b) was successful, a 100% molar excess of the halide was mixed with the pyridine in acetone in a stoppered flask and allowed to stand at room temperature. The solid precipitate which resulted was periodically separated by filtration and purified by recrystallization.

TABLE I

PROPERTIES OF 3-SUBSTITUTED PYRIDINIUM SALTS



Compound No.	Substituents R	R'	X^-	Melting Point (°C) Observed	Literature
2	CH_3	$CO_2C_2H_5$[a]	I	136-139	138-140[14]
3	CH_3	COPh	I	151-153	
4	CH_2Ph	COPh	Cl	178.5-179.5	177-179[16]
5	DCB[b]	COPh	Cl	172-173	
6	CH_3	$COCH_3$	I	165-166	163-164[48]
7	CH_2Ph	$COCH_3$	Cl	188-189	185.5-186[32]
8	DCB[b]	$COCH_3$	Cl	181-181.5	
9	CH_3	CN	I	197-198	198[33]
10	CH_2Ph	CN	Cl	191-191.5	
11	DCB[b]	CN	Cl	164-166	
12	CH_3	CN,5-CH_3	I	287-289	
13	CH_2Ph	CN,5-CH_3	Br	175-177	
14	DCB[b]	CN,5-CH_3	Cl	172-172.5	

Table I (continued)

Compound No.	Substituents R	R'	X^-	Melting Point (°C) Observed	Literature
15	CH_3	$CONH_2$	I	205.5-207	202.7-203.4[30]
16	CH_2Ph	$CONH_2$	Cl	238-239.5	235-236[32]
17	DCB[b]	$CONH_2$	Cl	235-238	
18	CH_3	CO_2CH_3	I	131-132.5	127.5-128.5[30]

[a] 5-Bromo. [b] DCB = 2,6-Dichlorobenzyl.

Table I (continued)

Comp. No.	Preparation Method	Yield (%)	R.S.[c]	Calculated (%) Carbon	Calculated (%) Hydrogen	Found (%) Carbon	Found (%) Hydrogen	Anal. By
2	(a)	42[d]	e	-	-	-	-	
3	(a)	91	f	48.02	3.72	48.02	3.73	W & S
4	(b)	60	f	73.66	5.21	74.00	5.43	F & M
5	(c)	77	-	60.26	3.73	60.45	3.83	F & M
6	(a)	87	f	-	-	-	-	
7	(b)	50	g	-	-	-	-	
8	(c)	92	-	53.11	3.82	52.94	3.74	Sch
9	(a)	82	f	-	-	-	-	
10	(b)	42	g	67.70	4.81	67.65	4.71	F & M
11	(c)	69	-	52.11	3.03	51.80	3.17	F & M
12	(a)	95	f	36.94	3.49	37.23	3.23	F & M

Table I (continued)

Comp. No.	Preparation Method	Yield (%)	R.S.[c]	Calculated (%) Carbon	Calculated (%) Hydrogen	Found (%) Carbon	Found (%) Hydrogen	Anal. By
13	(b)	90	f	58.14	4.53	57.78	4.51	F & M
14	(c)	77	-	53.61	3.54	53.61	3.54	Sch
15	(a)	75	f	-	-	-	-	
16	(b)	80	f	62.78	5.27	62.53	5.19	F & M
17	(c)	78	-	49.16	3.49	49.57	3.33	F & M
18	(a)	88	f	-	-	-	-	

[c] Recrystallization solvent. [d] Yield calculated from nicotinic acid. [e] Isopropyl alcohol.

[f] Acetone. [g] 1:1 Acetone-methanol.

Preparation of 3,5-Symmetrically Disubstituted Pyridines

3,5-Dicarboxypyridine (51). A solution of 5.0 g. of 3,5-dimethylpyridine and 35.0 g. of potassium permanganate in 250 ml. of water was boiled for 10 hr. The black precipitate of manganese dioxide was separated by filtration from the colorless aqueous layer and was triturated with 250 ml. of boiling water. The aqueous solutions were combined and evaporated under reduced pressure to approximately 100 ml. The aqueous solution was cooled in an ice bath and treated with small portions of concentrated hydrochloric acid until a solution of pH 5 was obtained. The white solid which resulted was separated by filtration and additional hydrochloric acid was added to the solution until a solution of pH 3 was obtained. The white precipitate was separated by filtration. The combined solids were dried in a drying oven and gave 3.05 g. (39%) of 51, m. p. 321-323° dec., which was identical in every respect with an authentic sample.

3,5-Dimethoxycarbonylpyridine (52). A dry sample of 5.0 g. of 51 was slowly added to a stirred 20 ml. sample of thionyl chloride and the mixture was heated under reflux for 24 hr. Excess thionyl chloride was evaporated under reduced pressure. The flask containing the pale yellow residue was cooled in an ice bath and the residue was treated with 15.0 ml. of anhydrous methanol in small portions. The addition of methanol to the residue caused a highly exothermic reaction. The solution was allowed to warm to room temperature and boiled for 24 hr. after which the excess methanol was evaporated under reduced pressure. The

solid residue was mixed with 100 ml. of warm water and the solution was treated with sodium carbonate until a neutral solution was obtained. The aqueous solution was extracted with 200 ml. of ether. The aqueous solution was treated with 3.0 g. of sodium carbonate and extracted with 200 ml. of ether. The combined ether extracts were evaporated under reduced pressure and gave a yellow solid which was recrystallized from methanol. This gave, in several fractions, 3.95 g. (68%) of 52 as off-white crystals, m. p. 81.5-83.5°, lit.[4] m. p. 84-85°.

1-Methyl-3,5-dimethoxycarbonylpyridinium iodide (53). A solution of 2.0 g. of 3,5-dimethoxycarbonylpyridine (52) and 6.0 ml. of methyl iodide in 40 ml. of acetone was heated with stirring for 18 hr. and cooled in an ice bath. The yellow precipitate which formed was collected by filtration. The reaction gave 3.30 g. (96%) of 53, m. p. 200.0-200.5° dec.

Anal. Calcd. for $C_{10}H_{12}INO_4$: C, 35.63; H, 3.59. Found (F&M): C, 35.71; H, 3.52.

IR Spectrum (No 3440-33): 3095 (m), 3020 (m), 2960 (m), 1730 (vs), 1720 (vs), 1430 (vs), 1350 (vs).

UV Spectrum λ_{max}^{MeOH} (log ϵ): 350 (2.46), 277 (3.65), 270 (3.57)

NMR Spectrum (No. 1444 in D_2O): 4.15 (singlet, 6 protons), 4.68 (singlet, 3 protons), 9.50 (triplet, 1 proton), 9.72 (doublet, 2 protons), J_{24}= 1.5 c.p.s.

3,5-Dicarbamoylpyridine (54). A dry sample of 10.0 g. of 3,5-dicarboxypyridine (51) was slowly added to 40 ml. of thionyl chloride with stirring and the mixture heated to boiling for 20 hr. Excess thionyl chloride was evaporated

under reduced pressure giving a pale yellow residue. A 3-necked flask was equipped with a Dewar condenser cooled with a Dry-Ice and acetone slurry, and was connected to a tank of ammonia gas. The flask was immersed in a Dry-Ice and acetone slurry. Ammonia gas was passed into the system until 20 ml. of liquid ammonia were collected. The liquid was stirred magnetically, and small portions of the pale yellow solid were added to the flask via the third neck. The reaction was highly exothermic, and the system was cooled throughout the addition of the solid to the flask. After the addition of the solid was completed the resulting solution was allowed to stir for 1 hr. and the cooling devices were removed from the flask. The ammonia was allowed to evaporate leaving 10.0 g. of a dry white solid. The solid was added to 400 ml. of hot water to dissolve the inorganic contaminant, and the undissolved residue was separated by filtration giving a white solid which was dried in the drying oven. This gave 9.2 g. (92%) of 54, m. p. 311-313°, lit.[4] m. p. 303-304°.

1-Benzyl-3,5-dicarbamoylpyridinium Bromide (55). A solution of 2.0 g. of 3,5-dicarbamoylpyridine (54) and 3.0 g. of benzyl bromide in 5.0 ml. of diglyme (diethylene glycol dimethyl ether) was heated under reflux for 14 hr., and then was treated with 50 ml. of acetone. Heating was continued for 0.5 hr., and the solution was cooled in an ice bath. The yellow-tan precipitate was separated by filtration and washed with 300 ml. of ether. The sample was dried in the drying oven and gave 3.8 g. (95%) of 55, m. p. 261-262° dec.

Anal. Calcd. for $C_{14}H_{14}BrN_3O_2$: C, 50.01: H, 4.20 Found (Sch); C, 50.02; H, 4.45.

IR Spectrum (No. 3834-33): 3370 (s), 3190 (s), 3170 (s), 1690 (vs), 1605 (s), 1380 (s).

UV Spectrum λ_{max}^{MeOH} (log ϵ): 268 mμ (3.66)

NMR Spectrum (No. 1513 in warm D_2O): 9.70 (doublet, 2 protons), 9.49 (triplet, 1 proton), 7.73 (singlet, 5 protons), 6.23 (singlet, 2 protons), J_{24}= 1.8 c.p.s.

1-Methyl-3,5-dicyanopyridinium Iodide (56). A mixture of 1.0 g. of 3,5-dicyanopyridine and 3.0 ml. of methyl iodide in 25 ml. of acetone was heated under reflux for 6 hr. and cooled in an ice bath. The yellow precipitate which formed was separated by filtration. The solution was treated with 1.0 ml. of methyl iodide, was reheated for 24 hr., and was cooled in an ice bath. The solid which precipitated was collected by filtration to give a second fraction of product. The procedure was repeated three times and gave a total yield of 1.60 g. (76%) of 1-methyl-3,5-dicyanopyridinium iodide (56), m.p. 219-221° dec.

Anal. Calcd. for $C_8H_6IN_3$: C, 35.45; H, 2.23. Found (F&M): C, 35.51; H. 2.20.

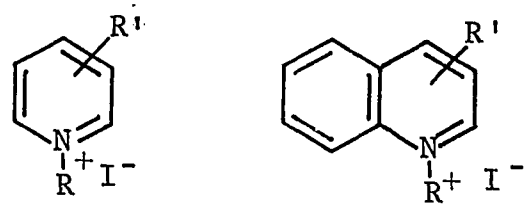
IR Spectrum (No. 3510-33): 3030 (s), 2945 (m), 2920 (m), 2260 (w), 1630 (m), 655 (vs).

UV Spectrum λ_{max}^{MeOH} (log ϵ): 348 (3.93), 288 (2.91), 280 (2.84), 247 (shoulder) (3.95).

NMR Spectrum (No. 1445 in warm D_2O): 9.92 (singlet, 2 protons), 9.62 (singlet, 1 proton), 4.68 (singlet, 3 protons).

TABLE II

OTHER QUATERNARY SALTS FOR CYANIDE ADDITION REACTIONS



Type A Type B

Compound No.	Type	R	R'	Melting Point (°C) Observed	Literature
19	A	CH_3	2-COPh	141-142	
20	A	CH_3	4-COPh	180-181	177-179
21	A	CH_3	2-CH_3	229-230	226-228[49]
22	A	CH_3	4-CH_3	152.5-154	149-150[49]
23[a]	A	CH_3	3,5-Ph,Ph	205-207	201-202[14]
24[a]	A	CH_3	4-CO_2CH_3	183-185[d]	184[d40]
25	B	CH_3	-	71-72.5	73[50]
26	B	CH_2Ph[c]	-	184-185[b]	182[54]
27	B	CH_3	2-Ph	193-194.5	197[52]

[a] Courtesy of P. S. Anderson. [b] Water free sample prepared by drying the sample at 100°C. [c] Bromide salt. [d] Decomposes.

TABLE II (continued)

Compound No.	Method	Preparation Time (hr.)	Yield (%)	Recryst. Solvent
19	(a)	6	92	g
20	(a)	1	79	g
21	(a)	1	89	g
22	(a)	3	95	g
23	-	-	-	h
24	-	-	-	e
25	(a)	1	82	e
26	(b)	48	79	g
27	(d)	-[f]	67	g

[e] Isopropyl alcohol. [f] One month. [g] Acetone. [h] Methanol.

1-Methyl-2-phenylquinolinium Iodide (27). The procedure for the synthesis of 2-phenylquinoline was that of Pfitzinger.[55] A mixture of 35.0 g. of 2-phenyl-4-carboxyquinoline and 7.0 g. of dry calcium hydroxide in a 200 ml. one neck flask was heated in a sand bath using a high temperature Fisher burner. The flask was equipped with a stillhead, condenser, and take-off adapter with a side arm. The still-head was heated with a heating tape, the condenser by passing steam through the outer jacket, and the take-off adapter with an infrared lamp. After heating the system for two hr., a suction was applied to the side arm and 2.0 ml. of forerun were collected and discarded. Distillation was continued for 1 hr. and two fractions of yellow oil were collected. These were combined and crystallized on cooling, yielding 20.7 g. of pale yellow solid. The solid was dissolved in hot ethanol and decolorized with charcoal (Norit). The ethanolic solution was cooled in an ice bath, and the solid product was isolated by filtration. This gave 18.0 g. (63%) of 2-phenylquinoline, m.p. 81.5-82.5°, lit.[52] m.p. 83°. This compound was quaternized by method (d) (Table II).

TABLE III

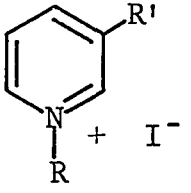
ULTRAVIOLET ABSORPTION SPECTRA OF QUATERNARY SALTS[a]

Compound No.[c]	λ_{max} (mμ)	log ε	Compound No.[c]	λ_{max} (mμ)	log ε
2	287	3.72	19	273	4.01[b]
				267	4.03
3	263	4.04	20	267	3.97
				258	3.92[b]
4	262	4.03	21	265	3.76
5	263	4.03	22	263	3.51[b]
				256	3.60
6	266	3.67	23	311	3.80
				257	4.42
7	263	3.60	24	275	3.63
8	267	3.63	25	315	3.96
9	269	3.59	26	317	3.93
10	269	3.58	27	328	4.24
11	270	3.65			
12	276	3.69			
13	277	3.65			
14	277	3.73			
15	265	3.61			
16	264	3.64			
17	267	3.66			
18	271	3.58[b]			
	265	3.65			

[a] Methanolic solutions. [b] Shoulder. [c] The structures of 2-27 are described in Tables I and II.

Table IV

NMR Spectra of Pyridinium Salts



Pyridinium Salt

Comp. No.	Substituents R	R'	Chemical Shift[a] R	2	3	4	5	6	C_6H_5 or $C_6H_3Cl_3$	Spin-Coupling Constant J_{45}	J_{56}	J_{46}	J_{24}
2	CH_3	CO_2Et[b]	4.66s	9.44d	1.58t 4.69q	9.25t	-	9.36d	-	-	-	1.8	1.8
3	CH_3	COPh	4.62s	9.18s[g]	7.87m	9.00d[g]	8.36q	9.34d[g]	-	8.0	5.5	*	*
4	CH_2Ph	COPh	5.99s	9.20d[g]	7.50m	8.80s$_x$	8.34q	9.33s$_x$	7.62m	8.2	6.0 J_{26}= 1.6	1.6	1.6
5	DCB[c]	COPh	6.28s	9.09s	7.50s	8.96d[g]	8.53q	9.34d[g]	7.65s	8.0	6.2	*	*
6	CH_3	$COCH_3$	4.72s	9.61s[g]	2.99s	9.23d[g]	8.47q	9.25d[g]	-	8.2	6.4	*	*
7	CH_2Ph	$COCH_3$	6.02s	9.52s[g]	2.84s	9.13d[g]	8.34q	9.19d[g]	7.57s	8.8	6.2	*	*
8	DCB[c]	$COCH_3$	6.35s	9.53d[g]	2.86s	9.12d[g]	8.36q	9.21s[g]	7.66s	7.8	6.6 J_{26}= 1.6	1.6	*
9	CH_3	CN	4.70s	9.65s[g]	-	9.17d[g]	8.50q	9.33d[g]	-	8.4	6.6	*	*
10	CH_2Ph	CN	6.05s	9.60s[g]	-	9.07s$_x$	8.42q	9.37s$_x$	7.64m	8.0	6.2 J_{26}= 1.6	1.6	1.6

Table IV (continued)

Pyridinium Salt

Comp. No.	Substituents R	R'	Chemical Shift[a] R	2	3	4	5	6	C_6H_5 or $C_6H_3Cl_2$	J_{45}	J_{56}	J_{46}	J_{26}
11	DCB[c]	CN	6.38s	9.54s[g]	-	9.17d[g]	8.47q	9.35d[g]	7.70s	8.4	6.8	*	*
12	CH_3	CN,5-CH_3	4.59s	9.42s[g]	-	8.97s[g]	2.74s	9.17s[g]	-	-	-	*	*
13	CH_2Ph	CN,5-CH_3	6.07s	9.45s[g]	-	8.92s[g]	2.76s	9.29s[g]	7.67m	-	-	*	*
14	DCB[c]	CN,5-CH_3	6.34s	9.30s[g]	-	8.98s[g]	2.75s	9.13s[g]	7.72s	-	-	*	*
15	CH_3	$CONH_2$	4.67s	9.45s[g]	-	9.06d[g]	8.36q	9.16d[g]	-	8.4	6.0	*	*
16	CH_2Ph	$CONH_2$	5.94s	9.39s[g]	-	8.95d[g]	8.24q	9.14d[g]	7.53s	8.2	6.0	*	*
17	DCB[c]	$CONH_2$	6.33s	9.41s[g]	-	9.09d[g]	8.38q	9.18d[g]	7.64s	8.2	6.2	*	*
18	CH_3	CO_2CH_3	4.80s	9.69s[g]	4.32s	9.25d	8.52q	9.37d	-	8.0	6.2	*	*

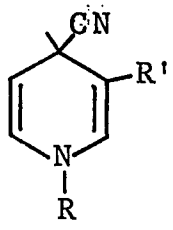
[a] In p.p.m. relative to DOH at 4.75 p.p.m. relative to tetramethylsilane. Solvent was D_2O.
[b] DCB= 2,6-Dichlorobenzyl. [d] Doublet. [g] With additional unresolved splitting. [m] Multiplet.
[o] Octet. [q] Quartet. [s] Singlet. [sx] Sextet. [t] Triplet. * Not observed.

Preparation of 4-Cyano-1,4-dihydropyridines.

The method employed for the preparation of 4-cyano-1,4-dihydropyridines was similar to that of Karrer, Marti, and Viscontini.[24] The addition of an aqueous solution of 0.03 mole of sodium cyanide to an aqueous solution of 0.01 mole of the pyridinium salt resulted in the precipitation of an oil or oily solid. In either case, the solution was decanted from the precipitate. The precipitate was washed with water to remove excess sodium cyanide. A single recrystallization of the precipitate from an appropriate solvent and drying the sample under reduced pressure gave analytically pure samples in good yield. In several cases, recrystallization caused decomposition of the sample and this step was eliminated from the procedure. Such unrecrystallized samples also provided satisfactory analyses. The properties of these 4-cyano-1,4-dihydropyridines are given in Table V.

TABLE V

PROPERTIES OF 4-CYANO-1,4-DIHYDROPYRIDINES



Comp. No.	Substituents R	R'	Melting Point (°C) Experimental	Literature
28	CH_3	$CO_2C_2H_5$[a]	145.5-147	
29	CH_3	COPh	109.5-110.5[d]	
30	CH_2Ph	COPh	115-116.5	113-115[16]
31	DCB[c]	COPh	156.5-158	
32	CH_3	$COCH_3$	117.5-118.5	113-123[56]
33	CH_2Ph	$COCH_3$	111-112	114-115.5[31]
34	DCB[c]	$COCH_3$	161-162[d]	154-156[19]
35	CH_3	CN	100-101	
36	CH_2Ph	CN	70-72	
37	DCB[c]	CN	126-128	128-130[19]
38	CH_3	CH,5-CH_3	92-93.5	
39	CH_2Ph	CN,5-CH_3	80-81[d]	
40	DCB[c]	CN,5-CH_3	136-138[d]	
41	CH_3	$CONH_2$	135[d]	125[d24]
42	CH_2Ph	$CONH_2$	145.5-148[d]	
43	DCB[c]	$CONH_2$	142-144[d]	146[19]
44	CH_3	CO_2CH_3	115-117	

TABLE V (continued)

Compound No.	Recryst. Solvent	Yield (%)	Calculated (%) Carbon	Calculated (%) Hydrogen	Found (%) Carbon	Found (%) Hydrogen	Anal. By
28	-b	75	44.29	4.09	44.55	4.04	F&M
29	ethanol	65	74.98	5.39	74.87	5.41	Sch
30	ethanol	63	-	-	-	-	
31	ethanol	72	65.05	3.82	65.07	3.94	Sch
32	ethanol	33	66.62	6.21	67.00	6.25	F&M
33	ether	43	75.61	5.92	75.90	6.10	F&M
34	ethanol	91	-	-	-	-	
35	none	83	66.19	4.86	66.15	4.63	F&M
36	ethanol	75	75.99	5.01	76.08	4.78	Sch
37	methanol	95	-	-	-	-	
38	none	94	67.91	5.70	68.05	5.73	F&M

TABLE V (continued)

Compound No.	Recryst. Solvent	Yield (%)	Calculated (%) Carbon	Calculated (%) Hydrogen	Found (%) Carbon	Found (%) Hydrogen	Anal. By
39	ethanol	70	76.57	5.57	76.75	5.48	Sch
40	-[b]	89	59.23	3.65	59.42	3.53	Sch
41	none	47	-	-	-	-	
42	none	87	70.27	5.48	70.47	5.70	F&M
43	none	92	-	-	-	-	
44	ethanol	55	60.66	5.65	60.20	5.34	F&M

[a] 5-Bromo. [b] 1:1 Methanol-ethanol solution. [c] DCB= 2,6-Dichlorobenzyl. [d] Decomposes.

1-Benzyl-3,4-dicyano-1,4-dihydropyridine (36). A solution of 2.0 g. of 1-benzyl-3-cyanopyridinium chloride (10) in 20 ml. of water was treated with a solution of 3.0 g. of sodium cyanide in 30 ml. of water. The yellow oil which formed was separated from the solution by decantation and was taken up in 100 ml. of ether. The ether was dried over magnesium sulfate and evaporated by heating on the steam bath. This gave a yellow oil whose ultraviolet absorption spectrum showed a single maximum at 330 mμ ($\log \epsilon = 3.84$) in methanol. Gas chromatographic analysis (Quadrol on KOH-washed Chromosorb W, 161°) showed only a single peak. The nuclear magnetic resonance spectrum was consistent with a 4-cyano-1,4-dihydropyridine (Table VII). The liquid crystallized after standing for three days in the cold, and was recrystallized from ethanol giving 1.35 g. (70%) of 1-benzyl-3,4-dicyano-1,4-dihydropyridine (36), m.p. 70-72° dec.

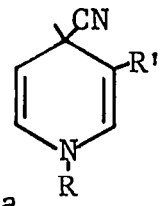
Anal. Calcd. for $C_{14}H_{11}N_3$: C, 75.99; H, 5.01. Found (Sch): C, 76.08; H, 4.78.

1-Methyl-3-benzoyl-4-cyano-1,4-dihydropyridine (29). A solution of 2.0 g. of 1-methyl-3-benzoylpyridinium iodide (3) in 20 ml. of water was treated with a solution of 3.0 g. of sodium cyanide in 30 ml. of water. A yellow oil precipitated immediately. The aqueous solution was decanted from the oil, and the oil was taken up in 100 ml. of ether. The ether was dried over magnesium sulfate and evaporated giving 1.10 g. of a yellow oil which darkened rapidly and solidified. The solid was isolated by filtration and recrystallized from warm ethanol. This gave 1.0 g. (65%) of 1-methyl-3-benzoyl-4-cyano-1,4-dihydropyridine (29), m.p. 109.5-110.5° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39. Found (Sch): C, 74.87; H, 5.41.

Table VI

Ultraviolet Absorption Spectra of 4-Cyano-1,4-Dihydropyridines[e]



Compound No.	R'	Chloroform[a] λ max	log ε	Methanol[b] λ max	log ε	Methanol[c] λ max	log ε
28	CO_2Et[d]	345	3.95	343	4.00	338	3.87
						262	3.60
29	COPh	355	4.10	361	4.16	360	4.13
30	COPh	353	4.11	357	4.12	357	4.10
31	COPh	351	4.11	355	4.10	355	4.08
				273	3.27	273	3.30
32	$COCH_3$	347	3.86	348	3.93	348	3.83
						266	3.04
33	$COCH_3$	343	3.96	347	4.00	347	3.97
				262	2.90	262	3.06
34	$COCH_3$	343	4.01	344	4.01	344	3.99
				273	3.03	273	3.04
35	CN	331	3.79	331	3.80	328	3.71
						277	3.20
36	CN	330	3.84	330	3.84	330	3.82
37	CN	328	3.84	327	3.83	327	3.82
				280	3.15	280	3.17
38	CN,5-CH_3	333	3.87	334	3.77	328	3.52
				284	3.19	284	3.44
39	CH,5-CH_3	333	3.84	332	3.83	328	3.74
				268	2.90	268	3.01
40	CN,5-CH_3	330	3.92	329	3.83	324	3.79
				280	3.16	280	3.30

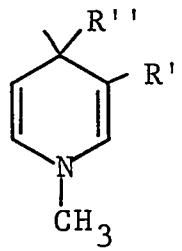
Table VI (continued)

Compound No.	R'	Chloroform[a] λ max	Chloroform[a] log ε	Methanol[b] λ max	Methanol[b] log ε	Methanol[c] λ max	Methanol[c] log ε
41	$CONH_2$	338	3.67	337	3.53	337	2.70
				265	3.42	265	3.62
42	$CONH_2$	335	3.80	334	3.65	334	3.39
				263	3.35	263	3.52
43	$CONH_2$	334	3.85	331	3.79	331	3.39
				273	3.27	274	3.50
44	CO_2CH_3	338	3.87	338	3.86	338	3.44
				265	2.95	265	3.51

[a]Spectra remained essentially unchanged after 90 min. Initial spectra were recorded 5 min. after dissolution of sample.
[b] Spectra were recorded 5 min. after dissolution of sample.
[c] Spectra were recorded 60 min. after dissolution of sample.
[d] 5-Bromo. [e] For the structure of R see Table VII.

Table VII

NMR Spectra of 4-Cyano-1,4-Dihydropyridines



Comp. No.	Substituents R	R'	R''	Chemical Shift[a] R	2	3	4	5	6	C_6H_5 or $C_6H_3Cl_2$	Spin-Coupling Constant J_{26}	J_{46}	J_{56}	J_{45}
28	CH_3	CO_2Et[b]	CN	3.16s	7.21d	1.28t 4.23q	4.73d	-	6.40q	-	1.6	0.5	-	-
29	CH_3	COPh	CN	3.05s	6.86d	7.43m	4.67d[g]	5.08q	6.01o	-	1.4	-[g]	7.8	4.8
30	CH_2Ph	COPh	CN	4.43s	7.05d	7.45m	4.74q	5.07q	6.14o	7.33m	1.6	0.8	8.8	4.6
31	DCB[e]	COPh	CN	4.72s	7.17d	7.48m	4.75q	5.06q	6.28o	7.38m	1.6	1.0	8.3	4.8
32	CH_3	$COCH_3$	CN	3.24s	7.19d	2.30s	4.65d[g]	5.04q	$6.10s_x$	-	1.4	*	7.6	4.6
33	CH_2Ph	$COCH_3$	CN	4.54s	-[c]	2.19s	4.57d	4.95q	6.09d[g]	7.33m	*	*	7.8	4.5
34	DCB[e]	$COCH_3$	CN	4.83s	7.38d	2.24s	4.58d	4.98q	6.25d	7.45m	1.7	*	7.5	4.6
35	CH_3	CN	CN	3.08s	6.70d	-	4.41q	4.78q	$5.98s_x$	-	1.4	0.9	8.2	4.4
36	CH_2Ph	CN	CN	4.38s	6.78d	-	4.42q	4.75q	$6.06s_x$	7.34m	1.6	1.4	8.0	4.2
37	DCB[e]	CN	CN	4.74s	6.87d	-	4.43q	4.81q	6.20o	7.43m	1.6	1.0	8.1	4.2
45	CH_2Ph	CN	H	4.23s	6.54d	-	3.10q	$4.65s_x$	5.71o	7.32m	1.6	1.4	8.4	3.6

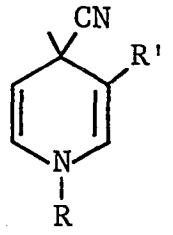
Table VII (continued)

Comp. No.	Substituents R	R'	R''	Chemical Shift[a] R	2	3	4	5	6	C_6H_5 or $C_6H_3Cl_2$	Spin-Coupling Constant J_{26}	J_{46}	J_{56}	J_{45}
38	CH_3	CN,5-CH_3	CN	3.07s	6.73d	-	4.29s[g]	1.78m	5.82q	-	2.1	*	~.5	-
39	CH_2Ph	CH,5-CH_3	CN	4.31s	6.76d	-	4.20s	1.66m	5.80m	7.26m	2.1	*	~.5	-
40	DCB[e]	CH,5-CH_3	CN	4.72s	6.86d	-	4.27s[g]	1.78q	5.96q	7.43m	1.4	*	1.4	0.7
41[f]	CH_3	$CONH_2$	CN	3.03s	7.22d	6.88s[g]	4.52d	4.77q	6.23q	-	1.4	*	7.4	4.4
42[f]	CH_2Ph	$CONH_2$	CN	4.48s	-[c]	6.93s[g]	4.57d	4.80q	6.36d[g]	7.37m	*	*	7.8	4.4
43[f]	DCB[e]	$CONH_2$	CN	4.54s	7.15d	6.79s[g]	4.35d	4.61q	5.97q	7.34m	1.3	*	7.6	4.9
44	CH_3	CO_2CH_3	CN	3.12s	7.20d	3.77s	4.65q	4.88q	6.02o	-	1.4	0.8	7.8	4.8
46	CH_3	CO_2Et[b]	H	3.00s	7.00q[g]	1.26t 4.17q	3.41q[g]	-	6.08q	-	1.4	1.4 J_{24}= 0.6	-	-

[a] In p.p.m. relative to tetramethylsilane. Spectra were determined in deuterochloroform unless noted. [b] 5-Bromo. [c] Under phenyl peak. [d] Doublet. [e] DCB= 2,6-Dichlorobenzyl. [f] Determined in dimethylsulfoxide. [g] With additional unresolved splitting. [m] Multiplet. [o] Octet. [q] Quartet. [sx] Sextet. [t] Triplet. * Not observed.

Table VIII

Infrared Absorption Bands of 4-Cyano-1,4-dihydropyridines[a]



Comp. No.	Substituents R	R'	Spectrum No.	Position of Bands (in cm.$^{-1}$)								
28	CH_3	$CO_2C_2H_5$[e]	1117-33	3075s	3020w	2980s	2960w 2930w	2900w 2850w	2230m	1680vs	1600vs	-
29	CH_3	COPh	3293-33	3070m	3030vw	2975w	2925m	2880sh 2820w	2225m	1675vs	1615s	1580s
30	CH_2Ph	COPh	2142-33	3080w	3025vw	3000w	-	-	2225m	1675vs	1610s	1580s
31	DCB[d]	COPh	3150-33	3070w	3030w	2970w	-	-	2230m	1690s	1625s	1590sh
32	CH_3	$COCH_3$	2172-33	3100w	3030w	-	2930w	2850w	2220m	1680s	1630s	1580s
33	CH_2Ph	$COCH_3$	2316-33	3060w	3030w	-	2930w	2890w	2225m	1680s	1630s	-
34	DCB[d]	$COCH_3$	3146-33	-[c]	-	-	-	-	2230m	1680s	1630s	1590s
35	CH_3	CN	2143-33	3080w	3050w	2980w	2930w	-	2230m 2200vs	1680vs	1620w	1590vs
36	CH_2Ph	CN	3306-33	3075w	3045m	3010sh	2925w	2840w	2230m 2200vs	1680vs	1600vs	-
			Intensity:	w-m	w-m	w-m	w	w-m	m-vs	s-vs	s-vs	s-vs

Table VIII (continued)

Comp. No.	Substituents R	R'	Spectrum No.	Position of Bands (in cm.$^{-1}$)								
37	DCB[d]	CN	3147-33	3100vw 3075w	-	3000w	2965w	-	2230w 2200s	1680vs	1620w	1590vs 1580s
38	CH_3	CN,5-CH_3	2941-33	3075m	-	2970m	2930m 2920sh	2830w	2220w	1690vs	1600vs	-
39	CH_2Ph	CN,5-CH_3	3287-33	3070s	3030s	2980s	2930s	2880s 2750w	2230m 2205vs	1695vs	1615vs	-
40	DCB[d]	CN,5-CH_3	3149-33	3080m	3020vw 2995vw	2980vw 2965vw	2935w 2920w	-	2225w 2205vs	1690vs	1605vs	1580s
41	CH_3	$CONH_2$	2177-33	3425s	3340w	3280w 3150m	2920w	-	2230m	1685s 1665s	1605vs	-
42	CH_2Ph	$CONH_2$	2315-33	3450s	3325m	3275w 3175s	2930w 2770w	-	2225s	1680s 1665s	1600s	-
43	DCB[d]	$CONH_2$	3148-33	3430s	3330w	3270w 3160mb	2950w	2850w 2725w	2230m	1680vs	1605vs	1580s
44	CH_3	CO_2CH_3	2173-33	3080m	3050w	3000w	2960m	2870m	2230s	1680s	-	1590s
			Intensity:	w-m	w-m	w-m	w	w-m	m-vs	s-vs	s-vs	s-vs

Table VIII (continued)

Comp. No.	Position of Bands (in $cm.^{-1}$)												
28	-	1470s	-	1435sh	1390sh	1375s	1355sh	1310s	-	1230vs	1205vs	-	-
29	1570s	1475m	1450m	-	1400s	1370s	1330s	1285m	1250vs	1210s	-	1180m	1160w
30	1565s	1490s	1450s	1430s	1390m	1370s	1350s 1330s	1300m	1265s	1220s	1195m	1180s	1165m
31	1575vs	-	1450s	1430s	-	1375s	1340s	1280s	1260s	1225s	1205sh 1195s	1190m 1170m	1155sh
32	-	1470m	-	1410m	-	1370m	1330m	1290m	1255s	-	1205s	1185m	-
33	1570s	1490w	1450w	1420m	-	1375m	1350w 1330m	-	1255s	-	1205s	1190sb	1175sb 1165sb
34	-	1460m	1440m	1425s	-	1375s	1350w 1320m	1280m	1250m	1225m	1200m	1190m	1180sh 1170m
35	-	1470s	-	1410s	1390s	-	1350s	1290s	-	1230s	-	1190s	-
36	-	1500m	1460m 1440m	1420s	1395s	1370m	1350m	1300m 1280m	-	1235s 1220s	-	1185vs	-
	s-vs	m-s	m-s	m-s	m-vs	m-s	w-s	w-s	m-s	m-s	m-s	m-s	m-vs

Table VIII (continued)

Comp. No.	Position of Bands (in $cm.^{-1}$)												
37	1565s	-	1450m	1430s 1420vs	1400s	1360m	1340m	1295m 1285s	-	1225s 1215s	-	1195sh	1185m 1170s
38	-	1475m	-	-	1400s	1385s 1370s	1350m	1280s 1270s	1255s	-	-	-	1160vs
39	-	1500s	1465vs	1430vs	1390m	1375s	1365sh	1300m	1265s	1210sb	-	-	1155s
40	1570s	-	1460s	1425vs	1390m	1380m	1350m 1310w	1285s	1265s 1255s	1220s	-	1195s	-
41	-	-	-	1420m	-	1375s	-	1290s	1260s	1220s	-	1180m	-
42	-	1495m	1450s	-	-	1380s 1360w	1350m	1300w 1285w	1265s	1225s	1210m	1185m	1165s
43	1560s	-	1450sh	1430m	1390vs	-	1360s	1310m 1280m	1260s	1220s	1205s	1190sh	1170s
44	-	1470m	1450s	1410s	1400s	1375s	1330s	1290m	1250s	-	1200s	-	-
	s-vs	m-s	m-s	m-s	m-vs	m-s	w-s	w-s	m-s	m-s	m-s	m-s	m-vs

Table VIII (continued)

Comp. No.	Position of Bands (in cm.$^{-1}$)														
28	1115sh	1090vs 1050s	-	1025m	985s	-	935s	910s	-	875m	855s	820s	765vs	730m	-
29	1130s	1075m	-	1015m	1000m	975s	945m 935s	925m	-	870s	850w	830m	790s	750m	720vs
30	1125s	1080s	-	1030s 1025s	1000s 995m	970s	940s	920s	900m	870s	840m	830s 825sh	790s	740s	720vs
31	1120s	1080m	1070w	1025m	1000w 990w	960m	940sh	930s 920sh	890vw	870m 860m	840m	820m	790vs 765m	740m 735m	720s
32	1115s	-	-	1050s 1030s	980s	-	945s	930s	880s	865s	-	-	-	745vs	720sh
33	-	1080s	1060m	1030s	990w	950s	-	915s	-	875s 860s	-	-	760s	735s	-
34	-	1085m	1055m	1030m	990w	970w	940s	915m	905m	880m	855m	820w	780s 770s	740m	730m
35	1130vs	1090m	1080m	1030s	985m	-	940m	920vs	900m	-	850vs	-	-	-	725vs
36	1150w	1080m	-	1025s	995w	975m	945w	920s	890m	855s	-	-	-	745s	-
	m-vs	m-vs	w-m	m-s	w-m	m-s	m-s	m-s	m-s	m-s	w-m	w-m	m-s	m-s	w-s

Table VIII (continued)

Comp. No.	Position of Bands (in cm.$^{-1}$)														
37	1145m 1115s	1080m	1065w	1020s	-	980m	955vs	915s	895w	860s	-	820m	780vs 765s	745s	730s
38	1140vs	1095vs	-	1010s	1000w	990m	950s	920vs	890vs	880vs	840w	-	-	-	720w
39	1135vs	1080m	-	1030m	985m	-	950m	915m	-	875m	-	820w	760m	740s	-
40	1145s 1130vs	1100w 1085m	1070w	1035w	1015m 980m	970w	955vs	915s	890w	880s	840w	825m	780vs 765vs	745s	720sh
41	1125s	1100sh	1065m	1020s	-	970w	-	925m 915s	890m	860s	-	-	785s	745s	730m
42	1120m	1070s	-	1020s	1000w 980m	970m	-	915s	900w	890s	870s	-	770m	740sb	730sb
43	1120s	1080m	-	1025s	-	970sh	955s	925m 915m	895s	865s	-	825m	780s 770s	745s	725m
44	1110m	1080s	-	1030s	990m	960s	-	-	890s	865s	-	-	775m 760w	745s	-
	m-vs	m-vs	w-m	m-s	w-m	m-s	m-s	m-s	m-s	m-s	w-m	w-m	m-s	m-s	m-s

[a] Mull in Halocarbon oil from 4000-1300 cm.$^{-1}$, in Nujol from 1300-650 cm.$^{-1}$.

[b] Broad. [c] No well defined bands in this region. [d] DCB = 2,6-Dichlorobenzyl.

[e] 5-Bromo. [m] Medium. [s] Strong. [sh] Shoulder. [v] Very. [w] Weak.

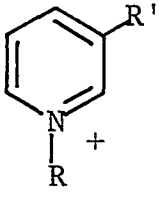
Studies of Cyanide Addition Reactions Using Ultraviolet and Visible Absorption Spectroscopy.

In order to detect the formation and isomerization of 6-cyano-1,6-dihydropyridines, the reaction of pyridinium salts with cyanide ion was studied by ultraviolet absorption spectroscopy. A 5.0 ml. aliquot of a freshly prepared methanolic solution of the pyridinium salt (10^{-4} molar) was rapidly pipetted into a 5.0 ml. aliquot of a freshly prepared methanolic solution of sodium cyanide (10^{-3} molar) in a 10.0 ml. volumetric flask. The flask was shaken vigorously for 30-45 sec. The solution was placed in the cuvette, and the ultraviolet absorption spectrum was scanned rapidly and repeatedly until no further changes in the spectrum were observed. The time at which mixing of the two solutions occurred was noted (time = 0 min.), and the time at the start of each determination of the spectrum was recorded.

The same procedure was repeated in the visible region of the spectrum. The results of these studies can be found in Table IX.

Table IX

Studies of Cyanide Addition to Pyridinium Salts in Methanol



Pyridinium Salt

Comp. No.	Substituents R	R'	Time[j] (min.)	First Run[a] λ_{max}	log ϵ	Intermediate Run[b] λ_{max}	log ϵ	Final Run[c] λ_{max}	log ϵ	Isosbestic Points (mμ)
2	CH_3	CO_2Et[i]	90	319	4.04	328	3.90	343	4.04	329
				262	4.18	262	4.00	262	3.61	
3	CH_3	COPh	45	425	2.63	425	2.62	425	2.62	415
				331	3.99	340	3.93	359	4.04	342
				282	3.88	280	3.72			
4	CH_2Ph	COPh	45	425	2.74	425	2.54	425	2.43	405
				332	4.08	347	4.01	358	4.10	343
				286	3.86	286	3.52			
5	DCB[h]	COPh	60	420	2.78	420	2.65	420	-[e]	405
				330	4.20	342	4.06	354	4.15	343
				282	3.97	282	3.72	282	3.43	
				273g	-	273g	-	273g	-	

Table IX (continued)

Pyridinium Salt Comp. No.	Substituents R	Substituents R'	Time[j] (min.)	First Run[a] λ_{max}	First Run[a] log ϵ	Intermediate Run[b] λ_{max}	Intermediate Run[b] log ϵ	Final Run[c] λ_{max}	Final Run[c] log ϵ	Isosbestic Points (mμ)
6	CH_3	$COCH_3$	30	410	2.53	345	3.89	350	4.06	396
				325	3.85					332
				270	3.78					
7	CH_2Ph	$COCH_3$	30	410	2.68	410	2.30	410	-[e]	390
				325	3.95	342	3.97	345	4.02	333
				270	3.71	270	3.22	270	2.74	
8	DCB[h]	$COCH_3$	30	405	2.90	405	2.67	405	1.85	385
				322	4.05	338	3.98	344	4.05	333
				281g	-	281g	3.51	281g	3.24	
				269	3.95	269	3.59	269	3.27	
9	CH_3	CN	45	372	3.11	372	2.93	331	3.76	360
				312	3.73	323	3.71			319
				253	3.52	253	3.27			
				245	3.77					
10	CH_2Ph	CN	45	370	3.16	370	3.00	329	3.81	358
				303	3.82	315	3.76	268	3.69	318
				252	3.78	252	-[f]	245	3.64	
				245	3.84					

Table IX (continued)

Pyridinium Salt Comp. No.	Substituents R	R'	Time[j] (min.)	First Run[a] λ_{max}	log ϵ	Intermediate Run[b] λ_{max}	log ϵ	Final Run[c] λ_{max}	log ϵ	Isosbestic Points (mμ)
11	DCB[h]	CN	45	370	3.24	370	3.12	324	3.86	354
				309	3.88	318	3.84	281g	3.36	318
				281g	3.57	281g	3.43	273g	-	
				273g	-	273g	-			
12	CH_3	CN,5-CH_3	30	323	3.80	332	3.86	333	3.86	321
13	CH_2Ph	CN,5-CH_3	30	318	3.89	327	3.90	331	3.92	322
14	DCB[h]	CN,5-CH_3	30	313	3.94	325	3.89	328	3.92	322
				281g	3.54	281g	3.40	281g	3.33	
				273g	-	273g	3.36	273g	3.30	
15	CH_3	$CONH_2$	10	334	3.30	-		337	3.59	286
				265	3.48			265	3.34	
16	CH_2Ph	$CONH_2$	10	331	3.59	-		333	3.80	290
17	DCB[h]	$CONH_2$	10	328	3.83	-		332	3.90	308
				281g	3.31			281g	3.27	
				273g	3.34			273g	3.27	

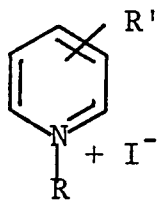
Table IX (continued)

Pyridinium Salt Comp. No.	Substituents R	R'	Time[j] (min.)	First Run[a] λ_{max}	log ϵ	Intermediate Run[b] λ_{max}	log ϵ	Final Run[c] λ_{max}	log ϵ	Isosbestic Points (mμ)
18	CH_3	CO_2CH_3	20	330 264 256	3.67 3.59 3.59	-		338	3.88	312

[a] Recorded between 1 and 1 1/2 min. after mixing. [b] Recorded approximately 1/4 to 1/2 through the total reaction time. [c] No important changes in the spectrum occurred after this determination. [d] Extinction coefficients (log ϵ) are subject to some variation due to the nature of the experimental conditions. [e] Very weak. [f] Less than previous value. [g] Shoulder attributed to phenyl absorption. [h] DCB= 2,6-Dichlorobenzyl. [i] 5-Bromo. [j] Total time during which the reaction was observed. Corresponds to final run[c].

Table X.

Pyridinium Salts Which Did Not React with Cyanide Ion[a,e]



Pyridinium Salt

Comp. No.	Substituents R	R'	Time[f] (hr.)	Spectrum of Pure Salt λ_{max}	log ϵ	Initial Spectrum λ_{max}	log ϵ	Final Spectrum λ_{max}	log ϵ
19	CH_3	2-COPh	-	273 267	4.01[d] 4.03	-		-	
20	CH_3	4-COPh	24	267 258	3.96 3.92[d]	267 258	3.92 3.88	267 258	3.92 3.88
21	CH_3	2-CH_3	24	265	3.76	265	3.80	265	3.80
22	CH_3	4-CH_3	24	263 256	3.51[d] 3.60	263 256	3.52 3.61	263 256	3.52 3.61

Table X (continued)

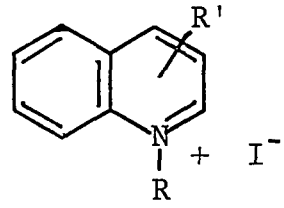
Pyridinium Salt

Comp. No.	Substituents R	R'	Time[f] (hr.)	Spectrum of Pure Salt λ_{max}	log ϵ	Initial Spectrum λ_{max}	log ϵ	Final Spectrum λ_{max}	log ϵ
23	CH_3	3,5-Ph,Ph	72	311	3.80	311	3.78	311	3.78
				257	4.42	257	-	257	-
24	CH_3	4-CO_2CH_3	72	275	3.63	275	3.68	263[b]	3.74

[a] Reactions were carried out with a sodium cyanide/quaternary salt ratio of 10/1. "DID NOT REACT" in the sense that no addition of cyanide ion to the pyridinium ion can reasonably be postulated from the evidence presented. [b] Isosbestic point at 294 mμ. [c] The spectrum was not determined. [d] Shoulder. [e] Reactions were run in methanolic solutions. [f] Corresponds to the time of determination of the final spectrum.

Table XI

Studies of Cyanide Addition to Quinolinium Salts[a,e] in Methanol



Quinolinium Salt

Comp. No.	Substituents R	R'	Time (min.)	First Run[b] λ_{max}	log ϵ	Intermediate Run[d] λ_{max}	log ϵ	Final Run λ_{max}	log ϵ	Isosbestic Points (mμ)
25	CH_3	-	30	314	3.88	302	3.96	299	4.07	312
				308[c]	3.86					249
26	CH_2Ph[f]	-	30	341[c]	3.19	341[c]	2.54	299	3.95	316
				316[c]	3.69	300	3.91			267
				304	3.73					
27	CH_3	2-Ph	30	328	4.09	313	3.80	378	3.00	361
				259	3.87	259	4.04	306	3.75	300
								258	4.16	247

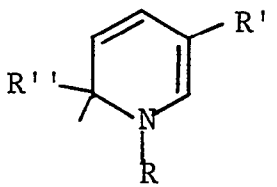
[a] Methanolic solutions. [b] Recorded approximately 1 to 1 1/2 min. after mixing of the two solutions. [c] Shoulder. [d] Recorded approximately halfway through the total reaction time. [e] Log ϵ values are subject to some variation due to the nature of the reaction conditions. [f] Bromide salt.

Studies of Cyanide Addition Reactions Using Nuclear Magnetic Resonance Spectroscopy

A solution of 2.0 g. of the quaternary salt in 20 ml. of water was treated with a solution of 3.0 g. of sodium cyanide in 30 ml. of water. The flask was stoppered, shaken vigorously, and the aqueous solution was discarded. The oil which remained on the bottom and sides of the flask was washed with water and taken up in 2.0 ml. of deuterochloroform. The nuclear magnetic resonance spectrum of the solution was determined rapidly and repeatedly until no further changes in the spectrum were observed. The procedure was timed as in the ultraviolet-visible absorption spectrum studies. The signals of the initially formed species in these reactions are described in Table XII.

Table XII

NMR Spectra of 6-Cyano-1,6-dihydropyridines



Comp. No.	Substituents R	R'	R''	Chemical Shift[a] R	2	3	4	5	6	C_6H_5	Spin-Coupling Constant J_{24}	J_{45}	J_{46}	J_{56}
47	CH_3	CO_2Et[b]	CN	3.11s	7.30s[g]	1.25t 4.18q	6.95q	-	5.27s[g]	-	0.9	-	0.4	-
48	CH_3	CO_2Et[b]	H	2.88s	7.27d	1.25t 4.16q	6.68q	-	4.28d	-	1.3	-	1.3	-
49	CH_3	CN	CN	4.41s	6.98q[g]	-	6.15s$_x$	5.10o	5.04d	7.34m	1.0	7.7	2.0	5.4 J_{26}= 1.0
50	CH_3	COPh	CN	4.45	7.30	7.40	7.00	5.25	5.16	7.40	-[e]	-	-	-

[a] In p.p.m. relative to tetramethylsilane. Spectra were determined in deuterochloroform. [b] 5-Bromo. [d] Doublet. [e] Coupling constants could not be determined. [g] With additional unresolved splitting. [m] Multiplet. [o] Octet. [q] Quartet. [s] Singlet. [sx] Sextet. [t] Triplet.

1-Methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28). A solution of 0.5 g. of sodium cyanide in 20 ml. of water was added to a solution of 1.0 g. of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) in 50 ml. of water, and the mixture was stirred for 5 min. The solid which precipitated was separated by filtration and was recrystallized from 20 ml. of a 1:1 methanol-ethanol solution, yielding 0.55 g. (75%) of 1-methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28), m.p. 145.5-147° dec.

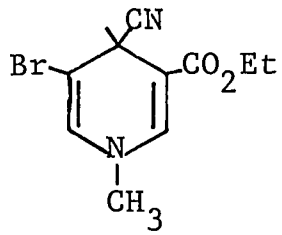
Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.29; H, 4.09; N, 10.33. Found (F&M): C, 44.55; H, 4.04; N, 10.63.

1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47). A solution of 3.0 g. of sodium cyanide in 30 ml. of water was rapidly added to a solution of 5.0 g. of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) in 50 ml. of water. The mixture was shaken for 1 min. and the water was decanted from the yellow oil (2*) which formed. Compound 2* was taken up in 75 ml. of warm carbon tetrachloride, half of which was then evaporated under reduced pressure. The solution was cooled in an ice bath. Four fractions of crystalline material were collected by filtration. The infrared spectrum of the third fraction is described in Table XIII and Spectrum 6. The third fraction consisted of 0.5 g. (13%) of 1-methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47), m.p. 140.5-142.5° dec. (begins discoloring at 130°).

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: C, 44.29; H, 4.09. Found (F&M): C, 44.77; H, 4.03.

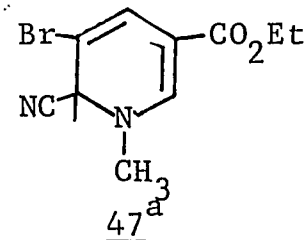
Table XIII

Infrared Spectra of 1-Methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28) and 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47)



28[c]

-[b]



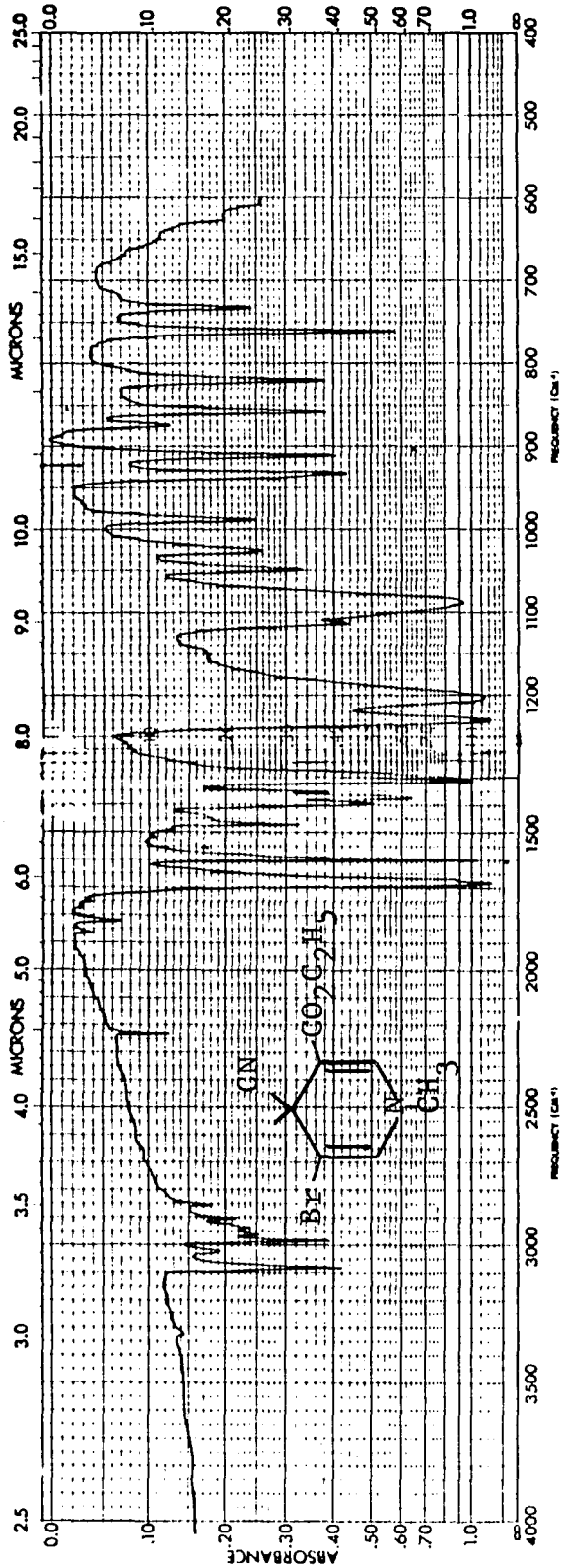
47[a]

3075 sx	-	3075 mx	1295 s	-	1295 s
-	1230 vs	3060 my	1240 vs	3060 my	1240 vs
3020 w	1205 vsx	-	1200 mx	-	1200 vwx
2980 s	-	2980 s	1170 vs	2985 s	1170 vs
2960 w	1115 m	2930 w	1115 w	2975 s	1120 wt
2930 w	1090 vs	2920 w	1080 vs	2935 w	1080 vs
2900 w	1050 sx	2900 w	1050 wx	2910 w	-
2850 w	1025 m	2850 w	1035 s	2870 w	1035 s
-	-	2800 w	1025 wt	2810 w	1020 wt
2230 m	985 sx	2225 w	990 wtx	2225 vw	-
1820 w	-	1820 w	965 sy	1790 w	965 sy
1680 vs	-	1685 vs	950 wt	1685 vs	950 wt
-	935 sx	1630 vsy	935 wx	1630 vsy	930 wtx
1600 vsx	910 sx	1600 sx	910 wx	1600 wx	-
-	-	1560 sy	895 vsy	1560 sy	895 vsy
1470 s	875 m	1470 m	875 w	1470 m	-
1435 mt	855 s	1430 m	855 s	1430 s	855 vs
1390 mt	-	1380 m	830 s	1380 m	830 s
1375 s	820 sx	1370 s	820 wtx	1370 s	-
-	760 vs	1360 wt	755 vs	1360 wt	760 s
1355 m	730 m	1350 wt	740 m	-	740 m
1310 s	-	1310 s	720 w	-	720 w

[a] Essentailly pure sample but possibly contaminated by a trace of the 1,4-dihydropyridine isomer (28). [b] Approximately 1:1 mixture of the 1,4- and 1,6-dihydropyridine isomers. This value was estimated by a comparison of the infrared absorption band intensities with those of 28 and 47. [c] Pure sample. [m] Medium. [s] Strong. [t] Shoulder. [v] Very. [w] Weak. [x] Absorption band characteristic of 28. [y] Absorption band characteristic of 47.

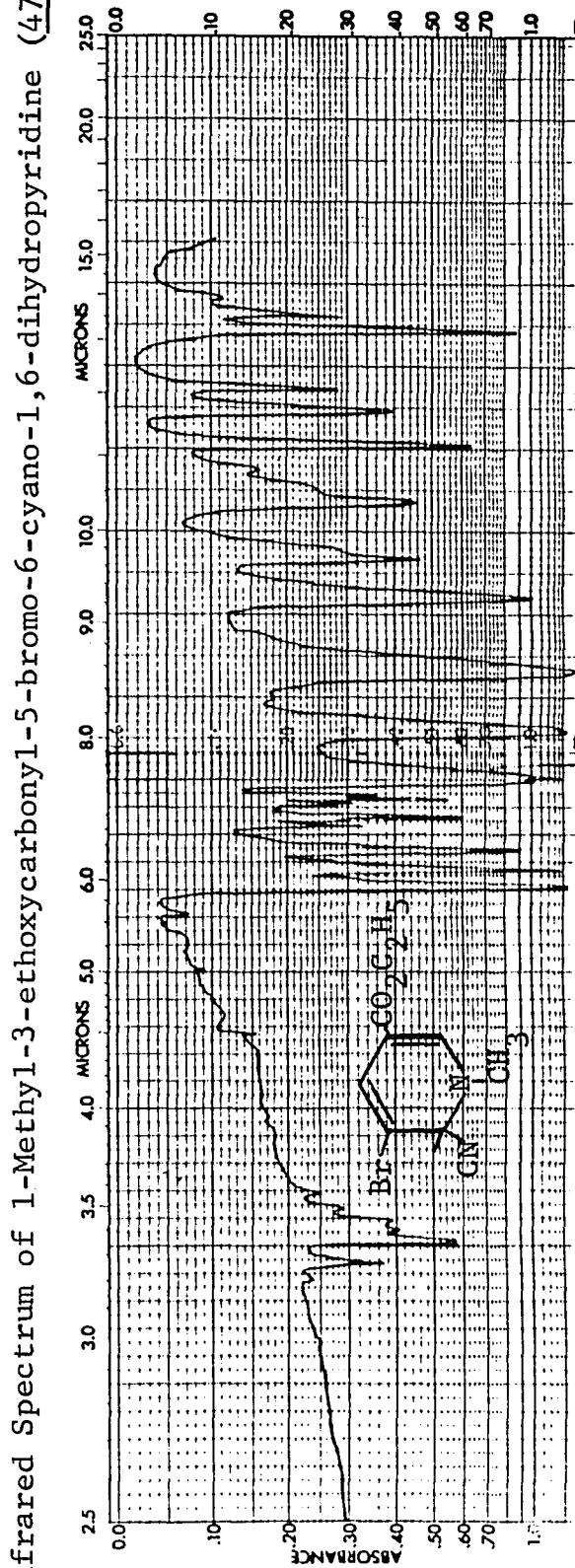
Spectrum 5

Infrared Spectrum of 1-Methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28)



Spectrum 6

Infrared Spectrum of 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47)



The Isomerization of 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47)

A solution of 2.0 g. of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) in 20 ml. of water was treated with a solution of 3.0 g. of sodium cyanide in 30 ml. of water. A yellow oil (2*) formed immediately. The aqueous solution was discarded, and the oil which remained on the bottom and sides of the flask was dissolved in warm ethanol. The solution was cooled in an ice bath, yielding a crystalline compound whose ultraviolet absorption spectrum showed a single maximum at 343 mμ in methanol identical with that of 1-methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28). A rapid determination of the ultraviolet absorption spectrum of a freshly prepared solution of 2* in methanol exhibited maxima at 321 mμ and 262 mμ (Table XVI). Both maxima diminished in intensity with time with the simultaneous formation of a single maximum at 343 mμ and only weak residual absorption at 262 mμ.

An identical reaction was run with the difference that the oil was taken up in 2.0 ml. of deuterochloroform. Rapid repetitive scanning of the nuclear magnetic resonance spectrum of this solution gave signals at 7.30 (singlet, 1 proton), 6.95 (quartet, 1 proton), 5.27 (singlet, 1 proton), 4.18 (quartet, 2 protons), 3.11 (singlet, 3 protons), and 1.25 (triplet, 3 protons) as indicated in Table XII and Spectrum 7. After 40 min., only signals characteristic of 1-methyl-3-ethoxycarbonyl-4-cyano-5-bromo-1,4-dihydropyridine (28) were observed as indicated in Spectrum 7.

Spectrum 7- Isomerization of 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47) in Deuterochloroform.

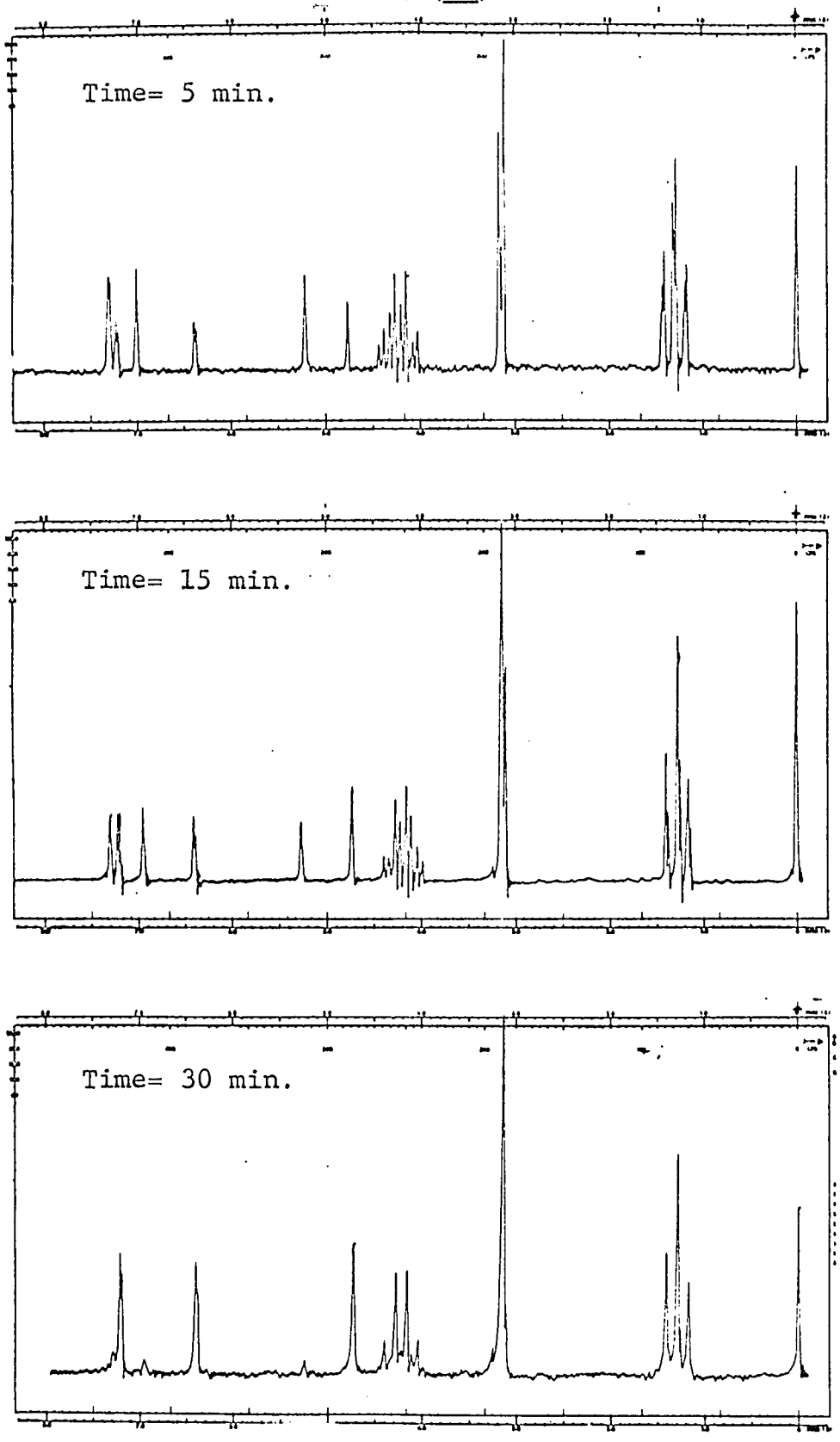


Table XIV

Ultraviolet Absorption Spectra of the Addition of Sodium Cyanide and Potassium Cyanide to 1-Methyl-3-ethoxycarbonyl-5-bromopyridinium Iodide (2)[a,b]

Metal Cyanide	Sodium Cyanide	Potassium Cyanide
Conc. of 2[c]	2.72×10^{-4}	2.72×10^{-4}
Conc. of M^+CN^-[c]	3.65×10^{-3}	3.47×10^{-3}

Run	Time (min.)	Maxima (mμ) and Extinction Coefficient							
1	1:00	320	8300	262	15700[d]	320	8300	262	15700[d]
2	4:00	321	7850	"	13800	322	7950	"	13400
3	7:00	323	7750	"	11750	323	7725	"	11500
4	10:00	324	7500	"	10450	324	7425	"	10150
5	13:00	325	7400	"	9350	325	7275	"	9725
6	16:00	326	7275	"	8400	327	7200	"	8250
7	19:00	327	7200	"	7575	328	7150	"	7575
8	22:00	329	7200	"	6900	329	7150	"	7050
9	25:00	330	7200	"	6250	330	7150	"	6475
10	28:00	331	7250	"	5725	331	7200	"	6175
11	31:00	333	7250	"	5350	333	7275	"	5800
12	34:00	335	7350	"	5000	334	7275	"	5500
13	37:00	336	7500	"	4700	335	7325	"	5300
14	40:00	337	7575	"	4400	336	7350	"	5025
15	43:00	338	7650	"	4200	337	7450	"	4850
16	46:00	338	7725	"	4050	338	7450	"	4700
17	49:00	339	7800	"	3850	338	7500	"	4600
18	52:00	339	7825	"	3700	338	7500	"	4500
19	55:00	340	7875	"	3600	338	7500	"	4400
20	58:00	341	7950	"	3500	339	7550	"	4350
21	61:00	341	7975	"	3400	339	7600	"	4275
22	76:00	342	8025	"	3100	339	7650	"	4075
23	90:00	342	8100	"	2950	339	7700	"	4050

[a] Reactions were run by mixing 5.0 ml. of the solution of 2 with 5.0 ml. of the solution of the metal cyanide.

[b] Methanolic solutions. [c] Moles/liter before mixing the two solutions. [d] Estimated.

Semi-quantitative Method for Studying the Rate of Isomerization of 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47) as a Function of Cyanide Ion Concentration. A 1.33×10^{-2} molar solution of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) in methanol was prepared. A 1.83×10^{-2} molar solution of sodium cyanide in methanol was also prepared. A 5.0 ml. aliquot of the sodium cyanide solution was pipetted into a 100 ml. volumetric flask. A 1.0 ml. aliquot of the solution of 2 was then added to the flask, and the moment of mixing of the two solutions taken as T = 0 min. The mixture was rapidly brought to volume (100 ml.) with methanol resulting in a solution whose initial concentrations were 1.33×10^{-4} molar in 2 and 9.15×10^{-4} molar in sodium cyanide. The ultraviolet absorption spectrum of the solution was rapidly determined. The time at which the absorbance of the 262 mμ maximum was recorded is noted in Table XV. The same procedure was repeated using 10.0 ml., 20.0 ml., and 50.0 ml. aliquots of the sodium cyanide solution with 1.0 ml. aliquots of the solution of 2.

It was assumed that formation of 1-methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47) is nearly quantitative and instantaneous under the conditions of the reaction because the absorbance of the 287 mμ region of the spectrum, corresponding to the quaternary salt, is essentially the same regardless of the cyanide ion concentration.

Table XV

Rate of Isomerization of 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47) as a Function of Cyanide Ion Concentration[a]

	Absorbance of 262 mμ Maximum			
Conc. of 2[b]	1.33×10^{-4}	1.33×10^{-4}	1.33×10^{-4}	1.33×10^{-4}
Conc. of NaCN[b]	9.15×10^{-4}	1.83×10^{-3}	3.66×10^{-3}	9.15×10^{-3}
Run	Time (Min.:Sec.)			
1	2:37	1.67	1.69	1.60	1.58
2	5:37	1.54	1.58	1.41	1.35
3	8:37	1.49	1.45	1.24	1.14
4	11:37	1.39	1.38	-	0.97
5	17:37	1.33	1.23	1.05	0.92
6	23:37	1.24	1.11	0.91	0.72
7	29:37	1.15	1.01	0.81	0.68
8	35.57	1.07	0.93	0.73	0.60
9	41:37	1.03	0.85	0.66	0.55
10	53:37	0.92	0.74	0.56	0.48
11	65:37	0.82	0.67	0.50	0.44
12	77:37	0.77	0.61	0.45	0.42
13	89:37	0.73	0.56	0.42	0.42
14	101:37	0.70	0.52	0.42	-

[a] Methanolic solutions. [b] Moles/liter.

Studies of the Isomerization of 1-Methyl-3-ethoxycarbonyl-5-bromo-6-cyano-1,6-dihydropyridine (47).[a,c] A Semi-quantitative Determination of the Rate of Isomerization of 47 as a Function of Solvent. Crystalline samples of 47 were dissolved in the solution described and their ultraviolet spectra were rapidly determined. The times at the beginning of each determination are recorded with the moment of dissolution of the sample taken as T = 0 min.

Table XVI

	λ_{max} (mμ) and Extinction Coefficients			
Solvent	Methanol	Methanol	95% Ethanol	95% Ethanol
Conc. of 47[b]	1.92×10^{-4}	2.02×10^{-4}	1.95×10^{-4}	1.95×10^{-4}
Conc. of NaCN[b]	none	2.29×10^{-3}	none	2.33×10^{-3}
Time (Min.:Sec.)				
1:00	321 6300 262 9475	321 7525 262 11000	321 7225 262 11000	322 7125 262 10600
5:45	321 6300 262 9375	323 7275 262 9400	322 7200 262 10400	323 6925 262 9550
9:45	322 6300 262 9275	325 7125 262 8075	322 7150 262 10000	324 6750 262 8625
15:00	322 6200 262 9075	327 7125 262 6925	323 7100 262 9550	326 6600 262 7650
20:00	322 6300 262 8900	330 7150 262 6000	323 7050 261 9150	329 6575 262 6875
25:00	- -	332 7225 262 5350	- -	332 6575 262 6150
30:50	- -	334 7350 262 4750	- -	- -
40:00	- -	337 7625 262 4100	- -	- -
45:00	- -	338 7675 262 3850	- -	- -

[a] Rate of isomerization can be estimated by following the rate of decrease in intensity of the 262 mμ maximum. There is no proof that compound 47 obeys Beer's Law. [b] Moles/liter.
[c] Reactions were not followed to completion.

PART II

SODIUM BOROHYDRIDE REDUCTION OF THE METHYL IODIDE SALTS OF FORMYL- AND BENZOYLPYRIDINE OXIMES, AND OXIME METHYL ETHERS

INTRODUCTION

Sodium borohydride is an extremely useful reducing agent in many organic reactions because it is unreactive toward a wide variety of protic and aprotic solvents and is selective in the reaction with many organic functional groups.[68] Carboxylic acids, acetals, acid anhydrides, esters, nitriles, carbon-carbon double bonds, and many other functional groups are generally resistant to reduction by sodium borohydride. Aldehydes, ketones, Schiff bases, and pyridinium ions are some of the numerous functional groups which are reduced by sodium borohydride. The mechanism of the sodium borohydride reduction of pyridinium salts has been the subject of extensive investigations in these laboratories[9-16] and has been found to proceed as described below. The references cited[9-16] contain reviews of most of the pertinent work that has been done in elucidating the mechanism of this reduction. The first step in the reduction involves attack of sodium borohydride at the 2-, 4-, and 6-positions of the pyridinium ion resulting in the addition of the elements of a hydride ion and producing 1,2-, and/or 1,4-, and/or 1,6-dihydropyridines. The relative amounts of reaction at the ortho and para positions has been shown to depend on the size of the N-substituent.[11] Although attack at positions ortho to the ring nitrogen is usually favored, increasing the size of the N-substituent appears to lead to an increase in the amounts of reaction at the para position as indicated in Part I of this thesis.

The second step in the reduction involves attack of a protonic species such as a solvated proton or protonic solvent (methanol, water) on the reactive enamine system generated in the first step of the reduction. The immonium ion generated in this step is rapidly reduced with the addition of a second hydride ion. Repetition of this procedure leads to reduction of the other enamine system if it is susceptible to reduction.

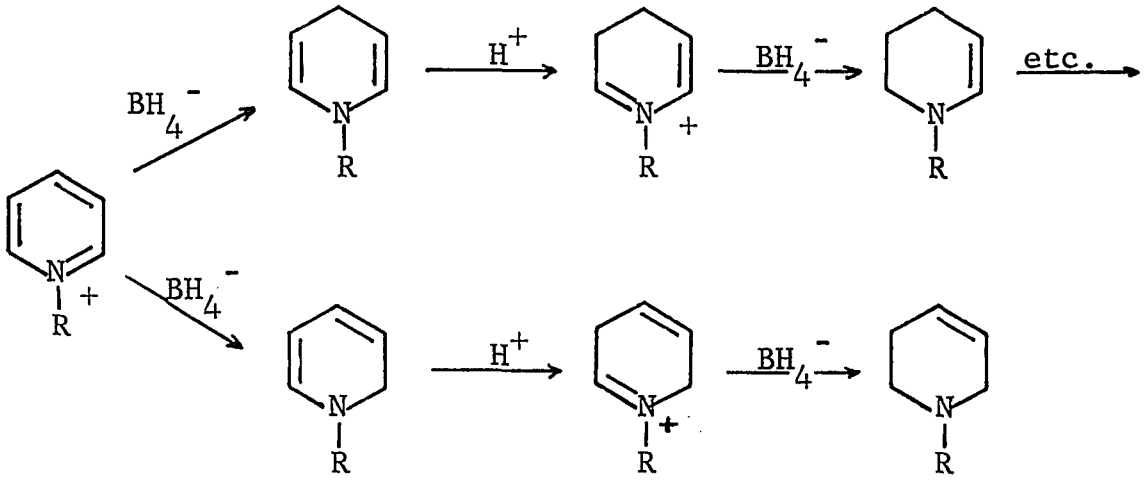


Figure 8. The Mechanism of the Sodium Borohydride Reduction of N-Alkylpyridinium Salts

Proton addition in the second step is a necessary condition for reduction beyond the dihydro stage since studies of the reduction in aprotic solvents such as dimethylformamide (DMF) or in strongly basic solvents[34-35] have been shown to lead to mixtures of stable dihydropyridines. Similarly, substituents located at the 3- and 5- positions of the pyridinium ion inhibit the attack of the proton at these positions, and the reduction of such ions usually results

in stable dihydropyridines.[9] The addition of protonic species and additional borohydride to these dihydropyridines may result in further normal reduction giving tetrahydropyridines or piperidines[9-11] as previously described. The nature of the ring substituents also influences the extent to which reduction will occur. For example, 1,2-dihydro- and 1,4-dihydropyridine isomers in which there is an electron-withdrawing substituent on the 3-position are usually resistant to further reduction.[9-16] The reader is referred to the work of Lyle et al[9-16] for a detailed discussion of these effects.

Many 1,2,5,6-tetrahydropyridines with electron-withdrawing substituents (formyl or ketones) on the 3- or 4-position, as well as the corresponding piperidines, are pharmacologically active[71] or capable of conversion to pharmacologically active agents by relatively simple reactions. The synthesis of piperidyl ketones or 1,2,5,6-tetrahydropyridyl ketones cannot be accomplished by catalytic reduction or sodium borohydride reduction, however, since pyridinium salts with formyl and ketone substituents are know to be reduced to alcohols by these reduction methods, with the reduction of the carbonyl function often proceeding more rapidly than the reduction of the pyridinium ring.[16] To avoid this problem, as well as to investigate the effect of the oximino function on the course of the sodium borohydride reduction, a series of oximino pyridinium salts were reduced with sodium borohydride. It was anticipated that protection of the carbonyl group by an oximation reaction, followed by reduction of the pyridinium ring with sodium borohydride, and regeneration of the carbonyl group by hydrolysis would provide a convenient method for the

preparation of 3- or 4-carbonyl-1,2,5,6-tetrahydropyridines as outlined below. A similar reaction scheme involving the use of lithium aluminum hydride as the reducing agent would probably not be satisfactory since it is known[68,74] that lithium aluminum hydride reduces the oximino function to the corresponding amine. In many cases, secondary amines are also isolated[68,74] from such reductions. A second aspect of this thesis, therefore, involved a general investigation of the reactivity of pyridinium oximes with sodium borohydride.

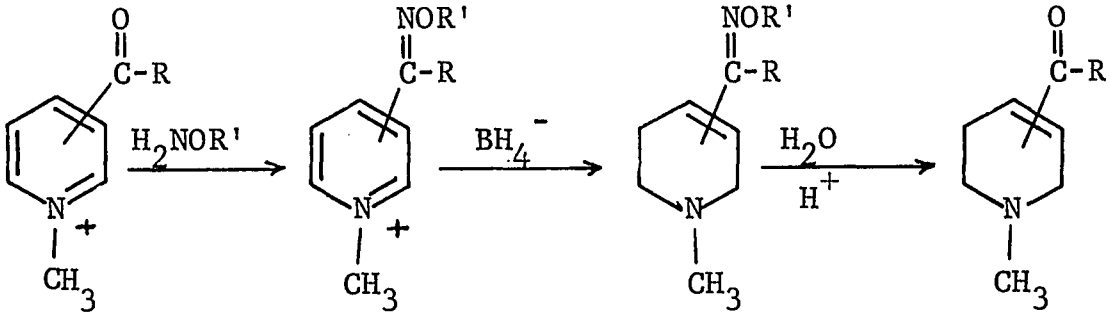


Figure 9. The Synthesis of 1-Alkyl-3-carbonyl-1,2,5,6-tetrahydropyridines from 1-Alkyl-3-carbonylpyridinium Salts.

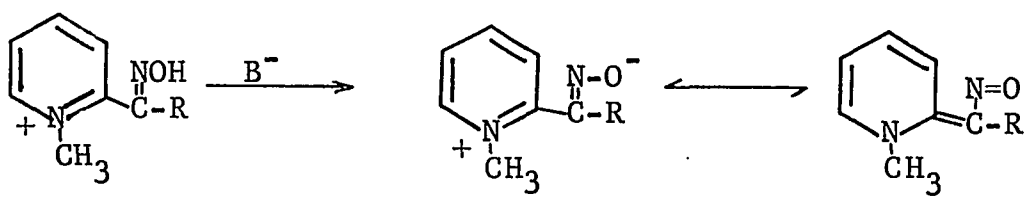
In addition to the preparation and reduction of a number of oximino pyridinium salts, many interesting observations concerning the chemical and spectroscopic properties of the pyridinium oximes and oxime, methyl ethers of a series of formyl and benzoyl pyridines were made, and the results of these studies comprise Part II of this thesis.

DISCUSSION AND RESULTS

Preparation of Pyridine Oximes and Oxime, Methyl Ethers and Their Methyl Iodide Salts (61-72).

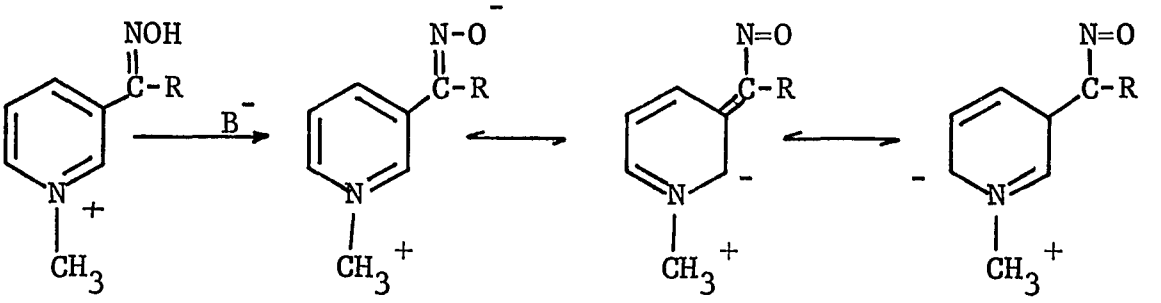
A number of oximino pyridinium salts were needed for these studies, and the preparation of a series of bases and methyl iodide salts of the isomeric formyl and benzoyl oximes and oxime, methyl ethers (61-72) was undertaken. They were prepared using known techniques[48,49,58] or modifications of known techniques. Their physical properties and microanalytical data are described in Table XVII and are in good agreement with the results of other studies.[48,49,58] Interestingly, the nature of the ultraviolet absorption spectra of the oximes and oxime, methyl ethers 61-72 were found to exhibit a marked dependence on the nature of the solvent. The ultraviolet absorption spectra of 61-72 in methanol are described in Table XVII. In general, the conversion of the oxime to the oxime ether caused no change in the ultraviolet absorption maximum in the 243-313 mμ region in methanol. In dimethylformamide, however, the oximes usually exhibited an additional strong maximum in the range 360-432 mμ which was not found in the corresponding oxime, methyl ethers. The appearance of the long wavelength maximum was accompanied by a decrease in the intensity of the lower wavelength maximum. The long wavelength maxima were attributed to the deprotonated zwitterionic form of the oxime as indicated below. That the deprotonation of the oximes occurred in dimethylformamide but not in methanol can easily be attributed to the higher basicity of the former solvent.[79] Ordinarily, simple

unconjugated oximes would not be deprotonated by a solvent as weakly basic as dimethylformamide. However, it should be noted that the oximino function is attached to the strongly electron-withdrawing pyridinium ion. The 2- and 4-oximino anions receive further stabilization by mesomeric interactions such as those shown below. These effects cause the oximes to be acidic and the anion to have a low energy electronic transition.



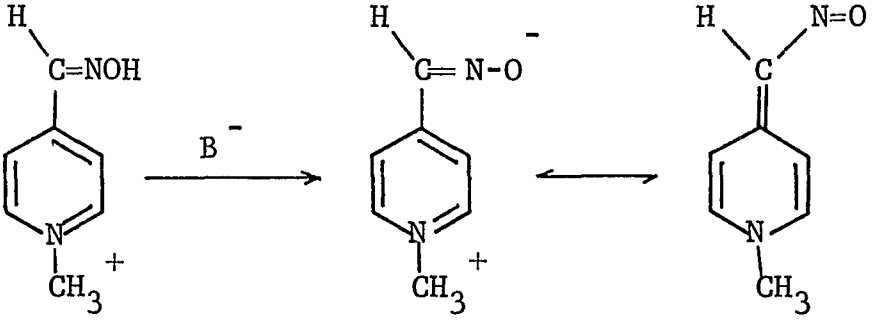
391-432 mu

The 3-substituted series should show similar acidity of the oximino function; however, the energy of electronic transition should be greater. No favorable resonance structures such as those in the 2- and 4-series can be drawn for the 3-series. As predicted, the ultraviolet absorption spectrum in dimethylformamide showed a second maximum due to the anion; however, it was at the high energy end of the 360-432 mμ region.



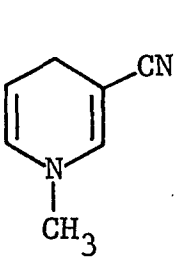
360-376 mμ

These observations were confirmed by the studies of several workers[58,69,70] who also found that the ultraviolet and infrared spectra of the three isomeric pyridine aldoximes and their methyl iodide salts depended on the basicity of the solvent. They found that strongly basic solvents caused the appearance of a prominent long wavelength maximum which was attributed to the resonance stabilized zwitterionic form of the pyridine oxime as described below.

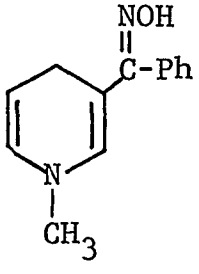


Sodium Dithionite Reduction of Pyridinium Salts

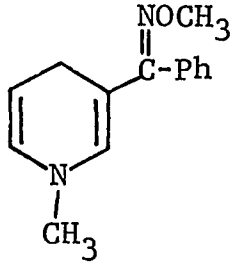
Since many 1,4-dihydropyridines have been shown to be intermediate in the reduction of some pyridinium salts with sodium borohydride, it was of interest to study the spectroscopic properties of such dihydropyridines. Stable 1,4-dihydropyridines were readily obtained from the sodium dithionite reduction of 3-substituted pyridinium salts by the method of Anderson and Berkelhammer.[31] The sodium dithionite reduction of 3-benzoylpyridine oxime methiodide (63) gave 1-methyl-3-benzoyl-1,4-dihydropyridine oxime (75), and a similar reduction of 3-benzoylpyridine oxime, methyl ether methiodide (64) gave 1-methyl-3-benzoyl-1,4-dihydropyridine, methyl ether (76). The sodium dithionite reduction of 1-benzyl-3-cyanopyridinium chloride (10) was accomplished by the method of Supple[15] and gave 1-benzyl-3-cyano-1,4-dihydropyridine (45).



45

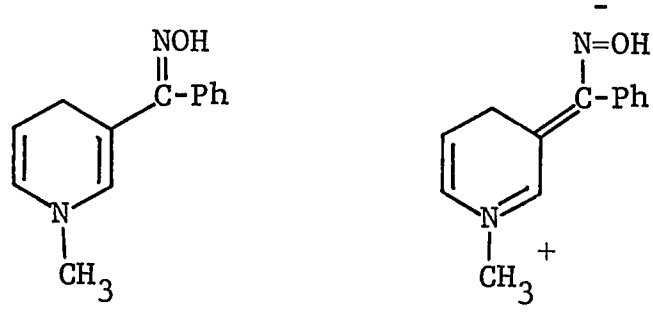


75



76

It has been shown[1,15,26] that the ultraviolet absorption maxima of 3-substituted-1,4-dihydropyridines is found at longer wavelengths as the polarity of the solvent increases. The spectra of 75 and 76 in a series of solvents of widely different polarity and dielectric constants also indicated a solvent dependence similar to that of 45 (Table XX). This effect presumably results from the increased interaction of polar solvent molecules with the polarized resonance form of the excited state of the dihydropyridines.[1] The resulting stabilization of the excited state of the dihydropyridine in polar solvents results in a decrease in the energy required for the ultraviolet electronic transition.[78]



The infrared spectra of 1-methyl-3-benzoyl-1,4-dihydropyridine oxime (75) and 1-methyl-3-benzoyl-1,4-dihydropyridine oxime, methyl ether (76) are described in Table XXII.

Sodium Borohydride Reductions of Pyridinium Salts

The feasibility of reducing the pyridinium oximes and oxime, methyl ethers with sodium borohydride was approached quite simply by a determination of the products from such reactions run on a synthetic scale. Only 3- and 4-substituted isomers were studied by this method. The sodium borohydride reduction of five pyridinium oximes and oxime, methyl ethers and the reduction of 1-methyl-4-styryl-pyridinium iodide (74) gave good yields of pure 1-methyl-1,2,5,6-tetrahydropyridine oximes in all cases. Yields of these products varied from 38-95% although no attempt was made to maximize yields. These results indicated that the oximino function behaved as other groups in determining the course of the reduction of the pyridinium ring. The effects of substituents in determining the course of the reduction of pyridinium ions have been described.[9-16] The properties of the 1,2,5,6-tetrahydropyridines 77, 78, 79, 80, 81, and 82 are summarized below, and their infrared spectra are described in Table XXII. The general course of the reaction is described below and the mechanistic pathway of the reductions has been discussed by Lyle.[9-16]

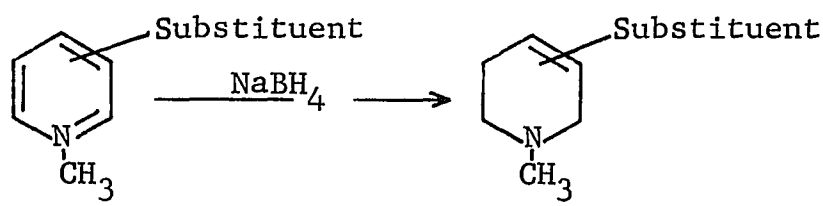


Figure 10. The Sodium Borohydride Reduction of Pyridinium Oximes and Oxime, Methyl Ethers.

While this work was in progress, Schenker and Druey[36] published the results of a similar study of the reduction with sodium borohydride of a series of 3- and 4-acetylpyridinium oximes with various N-substituents. In each case, they reported good yields of 1,2,5,6-tetrahydropyridine oximes which they described as useful parasympathomimetic agents. Their results complimented the above data in indicating the inertness of the oximino function towards sodium borohydride.

These studies confirmed that the preparation and reduction of pyridinium oximes and oxime, methyl ethers could be accomplished in good overall yield. The hydrolysis of the oxime was not attempted; however, standard methods for this type of reaction are available.[18,77]

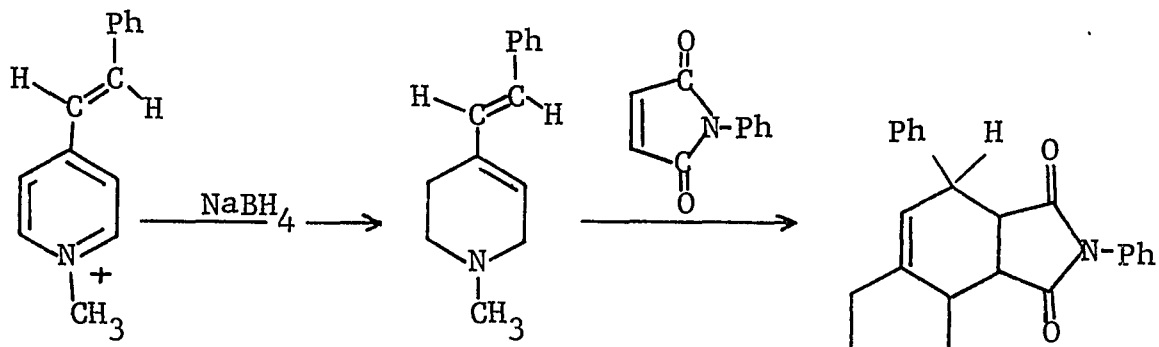
Sodium Borohydride Reduction of 1-Methyl-3-ethoxycarbonyl-5-bromopyridinium Iodide (2).

The sodium borohydride reduction of 2 had been studied by Anderson[14] and was found to give an 88% yield of a mixture of 1-methyl-3-ethoxycarbonyl-5-bromo-1,6-dihydropyridine (48) and 1-methyl-3-ethoxycarbonyl-5-bromo-1,4-dihydropyridine (46) in a 4:1 ratio. It seemed curious that none of the corresponding 1,2-dihydropyridine was ever observed since 1,2-dihydropyridines had been observed in the sodium borohydride reduction of similar[2,16,35] pyridinium ions. The reaction was repeated following Anderson's[14] method and the ultraviolet absorption spectrum of the unrecrystallized product was rapidly determined. The unrecrystallized sample exhibited maxima at 268 mμ and 354 mμ characteristic of 48, and in addition to these maxima, a weak maximum at 425 mμ ($\log \epsilon = 2.48$). This was attributed to 1-methyl-3-ethoxycarbonyl-5-bromo-1,2-dihydropyridine (84) since the model

compound 1-methyl-3-methoxycarbonyl-1,2-dihydropyridine showed an absorption maximum at 432 mμ (log ε=3.76).[34] The long wavelength maximum was not present in a recrystallized sample. These data indicate that only a small amount (6%) of the 1,2-dihydropyridine (84) was formed in the reaction. No attempts were made to isolate the 1,2-dihydropyridine (84).

Diels-Alder Reaction with 1-Methyl-4-styryl-1,2,5,6-tetrahydropyridine (82).

Another interesting synthetic reaction involved the Diels-Alder reaction of 1-methyl-4-styryl-1,2,5,6-tetrahydropyridine (82) with N-phenylmaleimide.



74 82 83

The reaction of 82, formed from the sodium borohydride reduction of 1-methyl-4-styrylpyridinium iodide (74), with N-phenylmaleimide was investigated as a means for the synthesis of phenyl isoquinoline derivatives. The Diels-Alder reaction of 82 with maleic anhydride failed; however, N-phenylmaleimide gave an adduct (83) whose microanalytical data and ultraviolet absorption spectrum were consistent only

with a normal Diels-Alder reaction product. The ultraviolet spectrum of 83 in methanol showed none of the strong absorption characteristic of 82 or N-phenylmaleimide but only absorption at 258 mμ and 268 mμ. The nuclear magnetic resonance spectra of 82 and 83 and the assignments of the signals are described in Table XXIII. The doublets centered at 6.76 p.p.m. and 6.44 p.p.m. in the spectrum of 82 had coupling constants of 16.4 c.p.s. This large coupling constant is consistent with trans exocyclic double bond but not with the cis isomer.[8] Compound 83 exhibited characteristic signals at 5.55 p.p.m. and 4.00 p.p.m. which integrated for one proton each and which were particularly useful in determining its structure. The former signal indicated a single vinylic proton[72] and the latter indicated a proton probably situated between two deshielding substituents, i.e. the phenyl and vinyl groups. The product from the Diels-Alder reaction (83) is particularly interesting because it contains many functional groups which can be utilized in converting 83 to other useful polycyclic compounds. The reaction of 82 with other dienophiles should lead to other adducts which may be useful as intermediates to other polycyclic compounds.

EXPERIMENTAL

Preparation of the Quaternary Salts of the Oximes and Oxime, Methyl Ethers of 2-, 3-, and 4-Formyl- and Benzoylpyridines.

(a) A solution of 0.05 mole of the formyl or benzoylpyridine and 0.08 mole of hydroxylamine hydrochloride in 40-60 ml. of 50% aqueous methanol was heated to boiling and a solution of 0.10 mole of sodium hydroxide in 50 ml. of 50% aqueous methanol was slowly added to it. The mixture was heated under reflux for 10-12 hr. The flask was cooled, the solid product was separated by filtration, and the solid was recrystallized from water or acetone. The oxime was dissolved in nitrobenzene and treated with a 30% molar excess of methyl iodide. The mixture was heated under reflux for 2 hr. and cooled in an ice bath. The oxime of the methyl iodide salt was separated by filtration and purified by recrystallization from acetone.

(b) Preparation of the oxime followed the method of (a). The oxime was dissolved in acetone or isopropyl alcohol and treated with a 30% molar excess of methyl iodide. The solution was heated under reflux for several hours, and was cooled in an ice bath. The oxime of the methyl iodide salt was separated by filtration and purified by recrystallization from an appropriate solvent.

(c) Preparation of the oxime followed the method of (a). The oxime was dissolved in acetone or isopropyl alcohol and was treated with a 100% molar excess of methyl iodide. The flask was stoppered and allowed to stand for 10-12 hr. The oxime of the methyl iodide salt was separated by filtration and purified by recrystallization from acetone or iso-

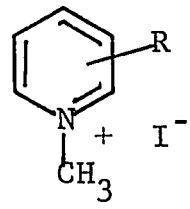
propyl alcohol.

(d) A solution of 0.033 mole of the formyl- or benzoylpyridine and 0.066 mole of methoxyamine hydrochloride in 20-40 ml. of ethanol was heated to boiling, and a solution of 0.075 mole of sodium hydroxide in 40 ml. of 50% aqueous methanol was slowly added to it. The mixture was heated under reflux for 10-16 hr., and cooled in an ice bath. The solution was extracted with several 100 ml. portions of ether. The combined ether extracts were evaporated under reduced pressure yielding a light yellow slurry or solid. This material was dissolved in acetone and a 50% molar excess of methyl iodide was added to it. The mixture was heated under reflux for several hours, and cooled in an ice bath. The methiodide of the oxime, methyl ether was separated by filtration and purified by recrystallization.

(e) A solution of 0.12 mole of 1-methyl-2-formylpyridinium iodide and 0.18 mole of hydroxylamine hydrochloride in 75 ml. of water was prepared and a solution of 0.18 mole of sodium hydroxide was slowly added to it. The flask was stoppered and allowed to stand for several days. The solvent was evaporated under reduced pressure, and the residue was taken up in 75 ml. of hot ethanol. The ethanolic solution was cooled in an ice bath. The 2-formylpyridine oxime methiodide which precipitated was pure and was collected by filtration.

Table XVII

Properties of Ring-Substituted Pyridinium Salts



Comp. No.	R	M.P. (°C)	Lit.M.P. (°C)	Preparation Method	Time (hr.)	Yield[a] (%)	R.S.[f]
61	2-C(=NOH)-Ph	195-197	195[48]	(a)	14	55	A
62	2-C(=NOCH3)-Ph	158-160		(d)	18	63	A
63	3-C(=NOH)-Ph	225-227	242[59]	(b)	14	67	A
64	3-C(=NOCH3)-Ph	225-230		(d)	14	72	A
65	4-C(=NOH)-Ph	205-207	215[48]	(c)	14	55	A
66	4-C(=NOCH3)-Ph	260-261		(d)	14	59	A
67	2-C(=NOH)-H	224-225.5	224[48]	(e)	48	50[c]	E
68	2-C(=NOCH3)-H	153-155	153[58]	(e)[d]	24	45	A
69	3-C(=NOH)-H	157-161	154[48]	(c)	14	18	A
70	3-C(=NOCH3)-H	163-165		(d)	14	54	A
71	4-C(=NOH)-H	178-181	181[48]	(c)	14	78	A
72	4-C(=NOCH3)-H	173-175	173[58]	(d)	12	15	A
73	2-CH=CHPh	234-235	229.5[49]		-	75	M
74	4-CH=CHPh	219-221	218[49]		-	90	M

Table XVII (continued)

Comp. No.	Empirical Formula	Calculated (%) Carbon	Hydrogen	Iodine	Found (%) Carbon	Hydrogen	Iodine
61	$C_{13}H_{13}IN_2O$	-	-	-	-	-	-
62	$C_{14}H_{15}IN_2O$	47.50	4.27	35.80	47.83	4.07	35.5
63	$C_{13}H_{13}IN_2O$	45.90	3.85	37.30	46.22	4.10	37.7
64	$C_{14}H_{15}IN_2O$	47.50	4.27	35.80	47.53	4.22	36.3
65	$C_{13}H_{13}IN_2O$	-	-	37.30	-	-	37.5
66	$C_{14}H_{15}IN_2O$	47.50	4.27	35.80	47.68	4.30	35.8
67	$C_7H_9IN_2O$	-	-	-	-	-	-
68	$C_8H_{11}IN_2O$	-	-	-	-	-	-
69	$C_7H_9IN_2O$	-	-	48.06	-	-	47.8
70	$C_8H_{11}IN_2O$	34.55	3.98	-	34.27	4.09	-

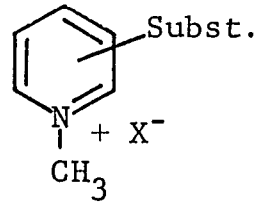
Table XVII (continued)

Comp. No.	Empirical Formula	Calculated (%) Carbon	Hydrogen	Iodine	Calculated (%) Carbon	Hydrogen	Iodine
71	$C_7H_9IN_2O$	-	-	48.06	-	-	47.8
72	$C_8H_{11}IN_2O$	34.55	3.98	-	34.53	3.99	-
73	$C_{14}H_{14}IN$	-	-	39.51	-	-	39.3
74	$C_{14}H_{14}IN$	-	-	39.51	-	-	39.6

[a] Represents overall yield calculated from formyl- or benzoylpyridine. [b] The determination of halogen was done titrimetrically using Mohr's method. [c] Estimated yield. [d] The method used was identical to that for 67 except that the methyl ether of the oxime was used in place of the oxime. [e] Analyses were by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. [A] Acetone. [E] Ethanol. [M] Methanol. [f] R.S.= Recrystallization solvent.

Table XVIII

Solvent Dependence of the Ultraviolet and Visible Absorption Maxima of Pyridinium Oximes and Oxime, Methyl Ethers[a]



Comp. No.	Substituent	Methanol λ max	Methanol log ε	DMF[b] λ max	DMF[b] log ε
61	2-C(=NOH)-Ph	296 256	3.63 4.02	432 312	3.70 4.06
62	2-C(=NOCH3)-Ph	307 264	3.46 4.11	357	3.66
63	3-C(=NOH)-Ph	313 243	3.28 4.15	360	3.11
64	3-C(=NOCH3)-Ph	257	4.23	-[c]	
65	4-C(=NOH)-Ph	307 252	3.60 4.18	423 305s	3.80 3.62
66	4-C(=NOCH3)-Ph	305 257	3.58 4.04	310s	3.47
67	2-C(=NOH)-H	298 250s	4.18 -	391 350	4.20 4.08
68	2-C(=NOCH3)-H	300 250s	4.20 -	324	3.72

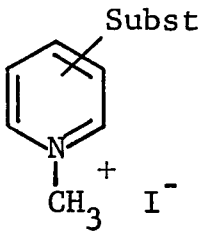
Table XVIII (continued)

Comp. No.	Substituent	Methanol λ max	Methanol log ε	DMF[b] λ max	DMF[b] log ε
69	3-C(=NOH)-H	297 257	3.70 4.10	376 300s	3.73 3.70
70	3-C(=NOCH$_3$)-H	302 265	3.65 4.00	328	3.58
71	4-C(=NOH)-H	286	4.27	412 283	3.98 4.11
72	4-C(=NOCH$_3$)-H	292	4.20	284	3.99

[a] Methyl iodide salts. [b] DMF= Dimethylformamide. [c] Spectrum was not recorded. [s] Shoulder.

Table XIX

Infrared Absorption Bands of Substituted N-Methylpyridinium Iodides[a]



Comp. No.	Substituents	Spectrum No.	Position of Bands (in cm.$^{-1}$)							
61	2-C(=NOH)-Ph	6063-21	3300--3000mb	-	2970m	2760w 2710w	-	1620m	1600m	1575m
62	2-C(=NOCH$_3$)-Ph	6066-21	3140w	3100--3000m	2890w	2960w 2920w	2800w	1620s	-	1575m
63	3-C(=NOH)-Ph	6071-21	3300--3000mb	-	-	-	2780w	1635m	-	-
64	3-C(=NOCH$_3$)-Ph	6072-21	-	3070w 3000w	2960w	2930w	2820w	1635m	1590w	-
65	4-C(=NOH)-Ph	6064-21	3300--3000wb	-	2980m	-	2760w	1640s	1610w 1600w	1570m
66	4-C(=NOCH$_3$)-Ph	6068-21	3140--3030w	3030--	2940m	2930w	2840w	1645s	-	1570m
67	2-C(=NOH)-H	6074-21	3200--3000sb	-	2950w	2840w 2700w	2600w	1625m	1590m	1580m
68	2-C(=NOCH$_3$)-H	6065-21	3050--3000w	2990m	2940w	-	2800w	1630m	1580s	1570sh

Table XIX (continued)

Comp. No.	Substituents	Spectrum No.	Position of Bands (in cm.$^{-1}$)								
69	3-C(=NOH)-H	6067-21	3400--3100mb	3020w	2960w	2920w	-	1640w 1620m	1585w	-	
70	3-C(=NOCH$_3$)-H	6069-21	-	-	3020m	2960w	2930w	-	1635m	1605m	1585w
71	4-C(=NOH)-H	6073-21	3300--3100wb	3020w	2950w	2840w	2700w	1640s	1610s	1570w	
72	4-C(=NOCH$_3$)-H	6070-21	3350w	3160w	3030w	2970w	2900w	2810w	1640m	1595s	1560w
73	2-CH=CHPh	3059-In	3050--2950vw	-	-	-	-	1625s	-	1570m	
74	4-CH=CHPh	2909-In	3050--2950vw	-	-	-	-	1650m 1630s	-	1570w	
	Intensity:		m-w	m-w	m-w	w	w	m-s	w-s	w-m	

[a] Mull in Halocarbon oil from 4000-1300 cm.$^{-1}$, in Nujol from 1300-650 cm.$^{-1}$.

[b] Broad. [m] Medium. [s] Strong. [sh] Shoulder. [w] Weak. [v] Very.

Table XIX (continued)

Comp. No.	Position of Bands (in $cm.^{-1}$)											
61	1515s	1495m	1455m	1395s	1330m	1280m	-	1185m	1175m	1030m 1010s	995sh	-
62	1515m	1495w	1455s	-	1335m	1275m	-	1180vs	1160vs	1040vs 1030s	990vs	-
63	1505m	1470vw	1445w	1390w	1330w	1290m	1210vs	1195m	1155m	1035w	1015s	995s
64	1510m	1495w 1465m	1445m	1345m	1330m	1285w	1220m	1190m	1165w	1055vs 1035m	1025s 1005m	995m
65	1525m	1500m 1465m	1450m	1395s	1330m	1280m	1220m	1200m	1165m 1150w	1080m 1030w	1005s	1000s
66	1525w	1500m 1470s	1450s	-	1340s	1285w	1230m	1205w	1170m	1055vs 1030s	1005m	995s
67	1505s	1465sh	1430m	1405sh	1320sh 1310s	1290m	1235m	1180s	1165m	-	1000vs	-
68	1515m	1465m	1440w	1405w	1360w	1290s	1250s	1175s	1165s 1120w	1055vs 1045vs	-	-
69	1505s	1475w	1440m	1410w	1335w	1295s	1250sh	-	1160s	1030w	990vs	-
70	1505m	1460m	-	1355w	1330m	1295s	1245w	1195w	1165s	1050vs	-	-
71	1520s	1470m	1430s	-	1330w	1285w	1230w	1190m	-	-	990vs	-
72	1520w	1470w	1435w	1390w	1330w	1285m	1235m	1195m	-	1045vs	975m	-
73	1520m	1460m	-	-	1330w	1300m 1280m	1220s	1185s	1175s	1045w	980vs	-
74	1525m	1480m	1460w	-	1340w	1300m	1215s	1190vs	1160w	1050w 1030m	975vs	-
	m-s	w-m	w-s	w-m	w-s	w-s	w-s	w-s	m-s	w-s	m-s	m-s

Table XIX (continued)

Comp. No.	Position of Bands (in $cm.^{-1}$)												
61	975w	950s 945sh	920w	895vw	-	810vw	780vs	750w	725m	695m	-	675w	650m
62	960vw	-	925vw	895s	835w	810m	780vs 790s	760w	730vw	690vs	670w	665m	640w
63	980w 965s	960s 940s	920vw	900w 890vw	855w 830m	815vs	760s	725sh	720s	695s	690s	680s	650w
64	-	945vw	930w	900vs	870w	815s	770m	-	725w	695s	685s	-	655m
65	970w 960w	940s	-	-	845vs	820s	775vs	-	720m	700s	680m	-	655s
66	980sh	935vw	-	890s	850s	820m	-	740vw	725m	700s	680vw	-	655m
67	-	940m	-	-	-	-	795m 780s	-	720m	-	-	-	655w
68	-	940s	-	910s	835w	-	785s 770vs	-	720m	-	-	-	640m
69	960w	940w	-	905w	-	820s	790s	-	720vw	-	675s	670s	-
70	-	930s	-	880m	-	815s	805s 780m	-	715w	-	675vs	655m	-
71	965m	945m	-	890vw	855vw	835s	790s	-	715w	690vw	-	-	660m
72	-	945s	-	870vw	-	845s	-	-	720w	-	-	-	-
73	-	-	-	890vw	860sh 850m	-	780vs 770vs	-	725m	-	680m	-	-
74	- w-m	- m-s	- w	880s w-s	- w-s	820s w-s	760s m-s	- w	715m w-m	- m-s	685s m-s	- m-s	- w-m

Preparation of 1,4-Dihydropyridines by the Reduction of Pyridinium Salts with Sodium Dithionite. The method used for the preparation of 1,4-dihydropyridines was essentially that of Anderson and Berkelhammer.[31]

Sodium Dithionite Reduction of 3-Benzoylpyridine Oxime Methiodide (63). A solution of 6.12 g. (0.018 mole) of 63 and 8.2 g. of sodium bicarbonate in 100 ml. of a 10-20% solution of methanol in water was prepared and cooled in an ice bath. The solution was treated with 11.7 g. (0.065 mole) of sodium dithionite with stirring and allowed to stand overnight. The product was isolated by filtration. Recrystallization of the solid product from 70 ml. of methanol gave 0.4 g. (11%) of 1-methyl-3-benzoyl-1,4-dihydropyridine oxime (75), m.p. 140-144° dec.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.58. Found (Sch): C, 73.20; H, 6.77.

Sodium Dithionite Reduction of 3-Benzoylpyridine Oxime, Methyl Ether Methiodide (64). The procedure was identical to that outlined above for the preparation of 75. The reaction gave 0.7 g. (20%) of 1-methyl-3-benzoyl-1,4-dihydropyridine oxime, methyl ether (76), m.p. 93-95° dec.

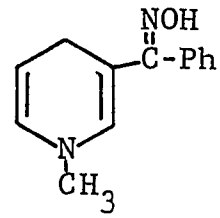
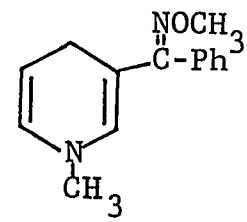
Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 73.65; H, 7:06. Found (Sch): C, 73.37; H, 7.11.

Sodium Dithionite Reduction of 1-Benzyl-3-cyanopyridinium Chloride (10). The method used for the preparation of 1-benzyl-3-cyano-1,4-dihydropyridine (45) was essentially that of Supple.[15] A solution of 4.14 g. of 10 and 8.2 g. of sodium bicarbonate in 60 ml. of water was cooled in an ice bath. The stirred solution was treated with 11.7 g. of sodium dithionite in small portions. The solution

was stirred for 1 hr. and the yellow precipitate which formed was separated by filtration. The solution was allowed to stand for 14 hr. at room temperature and the yellow precipitate was separated by filtration. The combined precipitates were washed with water and dried in a dessicator giving 2.65 g. (74%) of 1-benzyl-3-cyano-1,4-dihydropyridine (45), m.p. 55-56°, lit.[15] m.p. 54-55°.

Table XX

The Effect of Solvent on the Ultraviolet Absorption Maxima of 1,4-Dihydropyridines

Compound No.	75		76	
Structure				
Solvent	λ_{max}	log ϵ	λ_{max}	log ϵ
75% H_2O/25% MeOH	356	-	361	3.93
50% H_2O/50% MeOH	354.5	3.95	359	4.08
25% H_2O/75% MeOH	352	3.90	355	4.06
100% Methanol	349.5	3.99	351	4.09
Chloroform	352	3.98	355	4.03
Acetone	346	3.98	350	4.10
Iso-octane	343.5	-	346	4.06

Preparation of Tetrahydropyridines by the Reduction of Quaternary Salts with Sodium Borohydride

Sodium Borohydride Reduction of 3-Benzoylpyridine Oxime Methiodide (63). A solution of 10.0 g. (0.029 mole) of 63 in 150 ml. of 50% aqueous methanol was cooled in an ice bath. The solution was treated with 1.10 g. (0.029 mole) of sodium borohydride with stirring. The solution was extracted with several 100 ml. portions of ether. The ether extracts were combined and evaporated to 50 ml. by heating on the steam bath. The solution was cooled in an ice bath and a white solid precipitated. The solid was isolated by filtration and recrystallized from acetone to give 4.2 g. (65%) of 1-methyl-3-benzoyl-1,2,5,6-tetrahydropyridine oxime (77), m.p. 160-162°.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46. Found (Sch): C, 72.18; H, 7.76.

Sodium Borohydride Reduction of 4-Benzoylpyridine Oxime Methiodide (65). A solution of 10.0 g. (0.029 mole) of 65 in 100 ml. of 50% aqueous methanol was cooled in an ice bath. The solution was treated with 1.10 g. (0.029 mole) of sodium borohydride with stirring, and 100 ml. of water was added to the solution. Solid potassium carbonate was added until the solution reached a pH of 10. The solution was allowed to stand overnight and the yellow-white product which precipitated was isolated by filtration. Recrystallization of solid from acetone gave 6.0 g. (95%) of 1-methyl-4-benzoyl-1,2,5,6-tetrahydropyridine oxime (78), m.p. 151-153°.

Anal. Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46. Found (Sch): C, 72.10; H, 7.34.

Sodium Borohydride Reduction of 4-Benzoylpyridine Oxime, Methyl Ether Methiodide (66). A solution of 10.0 g. (0.0282 mole) of 66 in 100 ml. of 50% aqueous methanol was

cooled in an ice bath. The solution was treated with 1.07 g. (0.0282 mole) of sodium borohydride with stirring, and 100 ml. of water was added to it. The solution was extracted with four 100 ml. portions of ether. The ether layers were combined and evaporated by heating on the steam bath and the oily residue which remained was distilled at 4.7 mm. using a microdistillation apparatus. The material boiling from 153-155° was collected. This material crystallized upon standing for several days and gave 3.0 g. (51%) of 1-methyl-4-benzoyl-1,2,5,6-tetrahydropyridine oxime, methyl ether (79), m.p. 42-43°. Compound 79 was dissolved in anhydrous ether, and dry hydrogen chloride gas was bubbled slowly into the stirred solution. A white precipitate formed which was collected by filtration and recrystallized from ethyl acetate. This product was the hydrochloride of 79, m.p. 190-192°.

Anal. Calcd. for $C_{14}H_{19}ClN_2O$: C, 63.04; H, 7.18. Found (Sch): C, 62.84; H, 6.98.

Sodium Borohydride Reduction of 3-Formylpyridine Oxime Methiodide (69). The procedure was similar to that for the reduction of 71. The reaction gave 2.1 g. (38%) of 1-methyl-3-formyl-1,2,5,6-tetrahydropyridine oxime (81), m.p. 127-129°.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.98; H, 8.63. Found (Sch): C, 59.90; H, 8.62.

Sodium Borohydride Reduction of 4-Formylpyridine Oxime Methiodide (71). A solution of 10.55 g. (0.04 mole) of 71 in 30 ml. of water was cooled in an ice bath. The solution was treated with 1.56 g. (0.04 mole) of sodium borohydride with stirring and was extracted with three 100 ml. portions of ether. The ether layers were combined and the solvent was removed by evaporation by heating on the steam bath. The solid which remained was recrystallized

from acetone and gave 2.5 g. (45%) of 1-methyl-4-formyl-1,2,5,6-tetrahydropyridine oxime (80), m.p. 145-147°.

Anal. Calcd. for $C_7H_{12}N_2O$: C, 59.98; H, 8.63. Found (Sch): C, 60.21; H, 8.88.

Sodium Borohydride Reduction of 4-Styrylpyridine Methiodide (74). A solution of 10.0 g. (0.031 mole) of 74 in 80 ml. of 50% aqueous methanol was prepared and cooled in an ice bath. The solution was treated with 2.20 g. (0.06 mole) of sodium borohydride with stirring. The addition of 100 ml. of water caused the precipitation of a white solid which was isolated by filtration and dissolved in 100 ml. of ether. The solution was dried over potassium carbonate and the solvent was removed by evaporation under reduced pressure. This gave as residue 5.1 g. (82%) of 1-methyl-4-styryl-1,2,-5,6-tetrahydropyridine (82), m.p. 75-76°.

Anal. Calcd. for $C_{14}H_{17}N$: C, 84.37; H, 8.60. Found (Sch): C, 84.48; H, 8.76.

UV Spectrum λ_{max}^{MeOH} (log ϵ): 285 mμ (4.60), shoulders at 304, 298, and 285 mμ.

NMR Spectrum - Table XXIII.

Diels-Alder Reaction of 1-Methyl-4-styryl-1,2,5,6-tetrahydropyridine (82) with N-Phenylmaleimide. A solution of 1.0 g. (0.005 mole) of 82 and 1.72 g. (0.01 mole) of N-phenylmaleimide in 50 ml. of diglyme (diethylene glycol dimethyl ether) was heated to boiling for 24 hr. and concentrated by evaporation of the solvent under reduced pressure until its volume was approximately 25 ml. The solution was treated with 15 ml. of acetone and cooled in an ice bath. The brown precipitate which resulted was separated by filtration and dissolved in 30 ml. of hot acetone. This solution was decolorized with charcoal (Norit) and concentrated by evaporation at room temperature. This gave as residue 0.6 g. (32%) of a white solid (83), m.p. 188.5-189° which was dried for 2 days under vacuum.

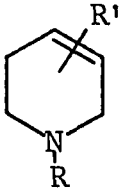
Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.50; N, 7.52. Found (F&M): C, 77.52; H, 6.80; N, 7.31.

UV Spectrum λ_{max}^{MeOH} (log ϵ): 268 mμ (2.70), 258 mμ (3.15).

NMR Spectrum- Table XXIII.

Table XXI

Properties of Ring-Substituted-1,2,5,6-tetrahydropyridines

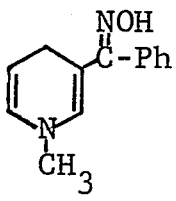


Compound No.	R	R'	Melting Point (°C)	Absorption Maximum λ_{max}	log ε
77	CH_3	3-C(=NOH)-Ph	160-162	241	3.74
78	CH_3	4-C(=NOH)-Ph	151-153	244	4.10
79	CH_3	4-C(=$NOCH_3$)-Ph	42-43	-	-
79·HCl	CH_3	4-C(=$NOCH_3$)-Ph	190-191	258	4.09
80	CH_3	4-C(=NOH)-H	145-147	229	4.27
81	CH_3	3-C(=NOH)-H	127-129	230.5	4.29
82	CH_3	4-CH=CHPh	77-79	285[b]	4.60

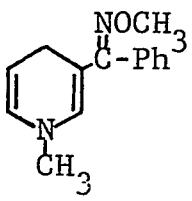
[a] Spectra were determined in methanol. [b] Shoulders at 304, 298, and 285 mμ.

Table XXII

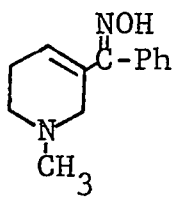
Infrared Absorption Spectra of Dihydropyridines, Tetrahydropyridines, and Their Derivatives[a]



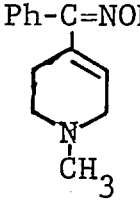
75



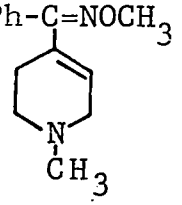
76



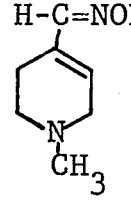
77



78



79



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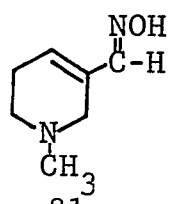
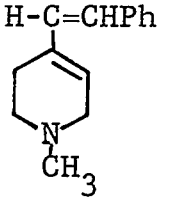
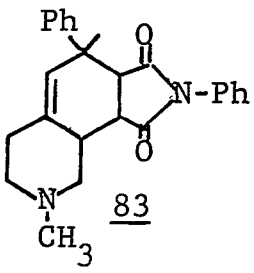


81



82



83

Comp. No.	Spectrum No.	Position of Bands (in cm.$^{-1}$)								
75	4562-21	3350--2800sb	-	-	-	1680s	1605vs	-	-	1475w
76	4560-21	3120--3040w	2960w	2870w	-	1680s	1610vs 1560m	1500m	-	1475w
77	3947-21	-	3020w	2920m	2860s	2830s	1640m	1620m	1520m	1490s	1460m
78	4564-21	-	3020---2500sb		1900---1825mb		1630w	-	1505s	1470m	1460m
79	4469-21	3040w	2950---2900s		2850w	2780s	-	1580w	1565w	1495m	1465s
79HCl	4583-21	-	3010---2960mb		2600---2400mb		-	1600w 1570w	1505m	1480s	1465s

Table XXII (continued)

Comp. No.	Spectrum No.	Position of Bands (in cm.$^{-1}$)									
80	3121-In	3200m	3100m	2925m	2800---2600sb 1800b		1650w	-	1510s	-	1460s
81	3267-In	3170s	3070s	2950m	2900---2770sb		1640m	1600m	-	1480s	-
82	2917-In	-	3000m	2925m	-	2700m	-	1600m	-	1485m	-
83	5796-In	-	3050w	2900m	2850w	2800m 1770m	1770vs	1590w	-	1490s	1460m
	Intensity	w-s	w-m	w-m		m-s	w-s	w-s	m-s	m-s	w-s

Table XXII (continued)

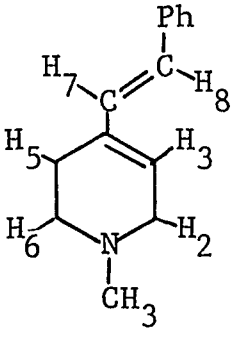
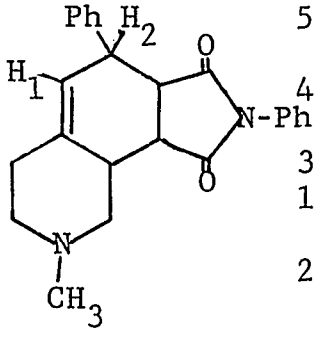
Comp. No.	Position of Bands (in cm.$^{-1}$)										
75	1440m	1400m	1380m	1340s	1305s	-	1220s	1185m	1140s	1080m	1070m
76	1450m	1410m 1390s	1380s	1340s	1300s	-	1225m	1185w	1145s	1090w	1050s
77	1430m	1410w	1360m	-	1300s	1270s	1200m	1170s	1150m 1130s	1090m	1080m 1060s
78	1450s	1430m 1390s	1325m	1315m	1300s	1265s	1200m	1155s	1135s 1125m	1075s	1060m
79	1445s	1430sh	1380s	1315m	1285s	1275s	1255s	1190m	1155s 1125s	1075sh	1050vs
79·HCl	1455s 1445s	1420m	1345w	1330m	1310s	1260m	1220w	1190s 1165s	1150s 1125s	1090m	1050sb
80	-	-	1370s	-	1300s	1280s	1260s	1200s	1130s	-	1070m
81	1440s	1415m	1365m	-	1300s	1285s	1255s	1200s	1130vs	1070s	1050s
82	1450s	1380s	-	-	1290s	1260s	1210s	-	1135s	1080s	1060m
83	-	1420w	1380s	-	-	1270s	1220s	1185s	1160s 1130m	1080m	1070s
Intensity	m-s	w-s	m-s	m-s	s	s	m-s	m-s	m-s	m-s	m-s

Table XXII (continued)

Comp. No.													
75	1030m 1015m	1000m	980s	945s	900m	890m 880m	845w	800s	770s	715s	710s	695s	660m
76	-	1000m	970m	930m	910m	890m	-	790m	775s	725m	715s	700m	655m
77	1050s 1040m	1000s	955s	925m	910m	885w	855w	800s	785w	770s	720s	705s	-
78	1035s	1005s	970vs	955s 925s	910s	-	835s	795m	760s	750s	720m	695vs	655s
79	1030s	-	995m 965s	955sh 935m	910w	870s 855w	825s	795w	-	765s	720w	690s	650m
79·HCl	1030s	1005s	980w	950s 935w	925w 910w	875s	855m 835s	800s	-	770vs	-	690vs	650s
80	1030m	-	980s	965s 940s	-	-	840s 820sh	790s	-	-	740s	-	-
81	1030s	1000sh	970vs	945vs 930s	-	880s 865s	-	-	-	775s	725s	-	-
82	1040s	-	990s 970vs	-	920m	-	830s	800s	-	750vs	730w	685s	-
83	1020s	1000m	-	950w	910w	890w 875s	850m 835s	-	785s	775m 765m	740vs 715s	700vs	-
Intensity	m-s	m-s	m-s	m-s	w-m	m-s	s	m-s	s	m-s	w-s	m-s	m-s

Table XXIII

NMR Spectra of 82 and 83

Structure	Chemical Shift[b]	Number of Protons	Assignment	Coupling Constant (cps)
 82	7.26m	5	C-Ph	
	6.76d	1	H_8	J_{78}= 16.4
	6.44d	1	H_7	J_{78}= 16.4
	5.77t	1	H_3	J_{23}= 4.0
	3.00q	2	H_2	J_{23}= 4.0
	2.47m	4	H_5, H_6	
	2.31s	3	N-CH_3	
 83	7.23m	10	C-Ph, N-Ph	
	5.55m	1	H_1	
	4.00m	1	H_2	
	3.61-1.61m	9	all other protons	
	2.35s	3	N-CH_3	

[a] Spectra were determined in deuterochloroform. [b] Chemical shift in p.p.m. relative to tetramethylsilane. [c] Determined by integration of peak areas. [d] Doublet. [m] Multiplet. [q] Quartet. [s] Singlet. [t] Triplet.

1-Methyl-3-ethoxycarbonyl-5-bromo-1,2-dihydropyridine (84). A solution of 15.0 g. of 1-methyl-3-ethoxycarbonyl-5-bromopyridinium iodide (2) and 18.0 g. of sodium bicarbonate in 250 ml. of water was cooled in an ice bath. The addition of 3.0 g. of sodium borohydride with stirring resulted in the precipitation of a dark orange solid. This crude product was isolated by filtration and was washed with water. A small amount of this solid was carefully dried in the air at room temperature. The ultraviolet spectrum of the unrecrystallized sample showed strong absorption maxima at 354 mμ and 268 mμ characteristic of 1-methyl-3-ethoxycarbonyl-5-bromo-1,6-dihydropyridine (48).[14] In addition to these two maxima, there was an additional weak absorption maximum at 425 mμ ($\log \epsilon = 2.48$). Recrystallization of the crude solid from methanol resulted in a crystalline product which did not exhibit the long wavelength maximum at 425 mμ. No attempts were made to isolate the compound responsible for the long wavelength absorption maximum. The long wavelength absorption is attributed to 1-methyl-3-ethoxycarbonyl-5-bromo-1,2-dihydropyridine (84). (See Discussion).

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BIOGRAPHICAL DATA

Name: George James Gauthier

Date of Birth: July 22, 1940

Place of Birth: Franklin, New Hampshire

Secondary Education: Franklin High School

Collegiate Institution Attended	Dates	Degree
University of Notre Dame	1958-1962	B. S.

Publications:

"Reactions of Nucleophiles with Pyridinium Ions. Cyanide Ion Reactions with Some Pyridinium Ions," with Robert E. Lyle, Tetrahedron Letters, 51, 4615 (1965).